Immune reconstitution inflammatory syndrome (IRIS):

Incidence, characteristics and predictive factors

Immune Reconstitution Inflammatory Syndrome (IRIS): Incidence, characteristics and predictive factors

A Dissertation submitted in partial fulfillment of the degree

M.D (General Medicine) Examination of

The Tamil Nadu Dr. M.G.R. Medical University, Chennai

August 2008.

CERTIFICATE

This is to certify that the dissertation entitled *"Immune reconstitution inflammatory syndrome (IRIS): incidence, characteristics and predictive factors"* is the bonafide original work of Dr. Deepti Gurdasani towards the M.D. Branch-1 (General Medicine) Degree Examination of the Tamil Nadu Dr. M.G.R University, Chennai to be conducted in 2009.

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ACKNOWLEDGEMENTS

I would like to express gratitude to my respected teacher and guide, **Prof**. **Anand Zachariah** for his valuable suggestions, meticulous guidance, support and encouragement in doing this study.

I am also grateful to **Prof. Dilip Mathai, Prof. O.C. Abraham** and all teachers in the **Department of Medicine** for all the support received in preparing this dissertation and throughout my three year course in General Medicine.

I would also like to thank Mr. Prasanna (Department of Clinical Epidemiology) who helped me with the analysis of the data.

I am grateful to **my parents** for their moral support and encouragement throughout my studies.

Last, but not the least, I thank all my **patients** for their co-operation in this study.

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Aims and Objectives

1. To study the incidence of immune reconstitution inflammatory syndrome (IRIS) in a cohort of HIV infected patients, newly initiated on highly active anti-retroviral therapy (HAART).
2. To describe the syndrome of IRIS.
3. To identify predictive factors for IRIS.

Literature review

Introduction:

Immune reconstitution inflammatory syndrome (IRIS) is the syndrome of paradoxical worsening of a known OI (OI) or appearance of signs of a new OI following initiation of highly active anti-retroviral therapy (HAART) in patients with Acquired Immunodeficiency Syndrome (AIDS). This is thought to result from restored immunity to specific infectious and non-infectious antigens. This phenomenon was first noticed when zidovudine monotherapy was associated with atypical and localised presentations in patients with *Mycobacterium avium intracellulare* (MAC)(1, 2). This was initially described in relation only to OIs but its definition has been expanded over the last few years to include certain autoimmune diseases such as grave's disease(3), rheumatic diseases(4), sarcoidosis(5) and malignancies(6). OIs associated with IRIS include tuberculosis(7-9), atypical mycobacterial infections(1), cytomegalovirus(CMV) retinitis(10), *Pneumocystis jirovecii* pneumonia(11, 12), herpes zoster(13), cryptococcal meningitis(14, 15), progressive multifocal leukoencephalopathy(PMLE)(16) and viral hepatitis(17). The manifestations of IRIS may be diverse depending upon the underlying OI and degree of inflammation. Introduction of ART has led to a significant decline in OIs associated with AIDS(18). However, delayed reconstitution of immunity may also contribute to OIs appearing within the first six months after initiation of ART which have to be distinguished from IRIS(19). The incidence of new OIs appears to be highest in the first three months following initiation of HAART. These may include OIs secondary to persistent immunodeficiency and OIs unmasked due to immune reconstitution(19).

Treatment of immunodeficient patients with highly active antiretroviral therapy (HAART) appears to restore pathogen-specific immune responses resulting in prevention

or regression of diseases caused by opportunistic pathogens. However restoration of pathogen specific immunity may be associated with paradoxical worsening and appearance of previously subclinical infections following initiation of ART, which is the phenomenon of IRIS(20). Many of these disease episodes are associated with the presence of a pathogen-specific immune response and a more exaggerated inflammatory response than is usually present in patients with OIs.

The overall incidence of IRIS is unknown, but may be dependent on the population studied and the background prevalence of OIs(21). Treatment for IRIS is largely supportive and includes treatment of the identified OI and use of anti-inflammatory agents such as steroids.

Several predictive factors for IRIS have been identified in small retrospective cohort studies. However, few prospective studies have been done to identify the risk factors for development of IRIS. In view of the diversity in presentation and incidence of IRIS between populations, local studies are required in India to examine its incidence, clinical characteristics and risk factors.

Types of IRIS

Jevtovic et al. described various OIs presenting as IRIS including dermatomal herpes zoster, pulmonary tuberculosis , tuberculous exudative pericarditis, tuberculous lymphadenitis, cerebral toxoplasmosis, PML, inflamed molluscum, inflamed *Candida albicans* angular cheilitis, genital herpes simplex, tinea corporis, CMV retinitis, CMV vitritis and HBV or HCV infection(22). In other retrospective studies also the spectrum of IRIS was similar(23, 24). Ratnam et al. also described cases of pneumocystis pneumonia and Kaposi's sarcoma presenting as IRIS(2). The following are the various types of infectious and non-infectious diseases associated with IRIS(20):

Table 1. Infectious and non-infectious causes of IRIS in HIV-infected patients

Infectious Etiologies	**Non-infectious etiologies**
Mycobacteria	Rheumatologic/Autoimmune
Mycobacterium tuberculosis	Rheumatoid arthritis Systemic lupus erythematosis(SLE)
Mycobacterium leprae	Graves disease , Autoimmune thyroid disease
Mycobacterium avium complex	Sarcoidosis & granulomatous reactions
Other mycobacteria	
Cytomegalovirus	AIDS-related lymphoma
Herpes viruses	Guillain-Barre syndrome (GBS)
Herpes zoster virus	Interstitial lymphoid pneumonitis
Herpes simplex virus	
Herpes virus-associated Kaposi's Sarcoma	
Cryptococcus neoformans	
Pneumocystis jirovecii pneumonia (PCP)	
Histoplasma capsulatum	
Toxoplasmosis	
Hepatitis B virus	
Hepatitis C virus	
Progressive multifocal leukoencephalopathy	
Parvovirus B19	

Strongyloides stercoralis infection & other parasitic infections

Molluscum contagiosum & genital warts

Adapted from Murdoch *et al. AIDS Research and Therapy* 2007

Epidemiology of IRIS

Several studies have attempted to study the incidence of IRIS. The incidence of IRIS depends on the underlying prevalence of OIs in a population, degree of immunodeficiency and other host genetic factors(20). The incidence of specific IRIS may also vary between different populations. The following are studies on patients to elucidate the incidence of IRIS and their characteristics:

Table 2: Epidemiological studies on IRIS

Authors	Place/ Country	Patients selected	Percentage of patients with IRIS	Duration of follow up	Median time of occurrence
Incidence studies on overall incidence of IRIS					
Puthanakit et al(25)	Thailand	Prospective study: HIV positive children with CD4 percentage <15% initiated on ART	19% (29/153)	48wks	4wks (2-31 wks)
Ratnam et al (24)	London, UK	Retrospective study: ART naive patients	22% (44/199)	6 months	12weeks(4-24wk)
M.A. French et al(23)	Perth, Australia	Retrospective study: HIV infected patients commencing	25% (33/132) among HAART	30 wks	<8wks in 67% patients

		HAART (naïve and experienced)	responders		
Jevtovic et al. (22)	Belgrade	Retrospective cohort: ART naive patients	16.7% (64/389)	----	4.6months(2-12)
Authors	Place/ Country	Patients selected	Percentage of patients with IRIS	Duration of follow up	Median time of occurrence
Incidence studies on OI specific incidence of IRIS					
Shelburne et al(26)	Houston, Texas	Retrospective cohort: HIV and M.Tb, M. avium and Cryptococcus coinfection	31.7% (57/180)	2.17 person years	46 days (3-658)
Narita et al (7)	Miami	Prospective cohort group1 HIV+TB initiated on ART	36% (12/33)	----	----
Bourgarit et al (27)	Paris, France	Prospective case series: 19 consecutive untreated HIV-TB coinfected patients	37% (7/19)	3months	-----
Kumaraswamy N et al (28)	Chennai, India	Prospective cohort study: HIV and TB co-infected patients commencing HAART	7.6% (11/144); 15/100 person years(incidence)	72 person years	42 days(10-89d)
Cheng et al (29)	Hong Kong	Prospective series: HIV and TB	15% (16/104)	---	56days (20-109)
Breton et al(30)	Paris, France	Retrospective study: ART naive patients with HIV and TB coinfection	43% (16/36)	2-65 months	12days (2-14)
Navas et al (31)	Spain	Retrospective study: HIV and TB co-infected patients	35% (6/17)	---	----
Lortholary et al. (32)	France	Retrospective multicentre study: HIV and cryptococcus co-infected patients commencing	Cryptococcal IRIS: 8.3% (10/120)	239 person years	8 months (2-37 months)

		HAART			

Incidence of IRIS in patients newly initiated on HAART varies from 16 to 25% (Table 2.). However, the incidence of IRIS in patients with HIV-TB co-infection may be variable ranging from 35 to 43%. There is only one prospective study from India which showed an incidence of 15 per 100 person years among patients with HIV-TB co-infection initiated on ART (28). (Table 2.)

Definitions of IRIS

The definition of IRIS has been a very controversial issue (21),(33). Most authors agree that IRIS is the new occurrence or clinical deterioration of an already existing OI in HIV-infected patients as a direct result of the enhancement of immune responses to those dormant pathogens during HAART. It occurs as an exaggerated immune response specific to endogenous antigens or pathogens rather than a new occurrence of exogenous OIs. The problem with the definition is the difficulty in establishing a causal relationship between initiation of HAART and onset of symptoms or signs. Worsening of symptoms and signs after initiation of HAART has to be distinguished from deterioration of OIs as a complication of residual immunodeficiency, inadequate treatment of primary OI or drug reactions.

Shelburne et al. laid down the first case definition for IRIS which has been adapted and used in several studies designed to assess the characteristics and incidence of certain

types of IRIS (32),(34). Recently, consensus case definitions have been laid down for paradoxical tuberculosis-associated IRIS, ART-associated tuberculosis, and unmasking tuberculosis-associated IRIS applicable to resource limited settings(35). The following are various definitions that have been used for IRIS in epidemiological studies:

Table 3. Definitions of IRIS used in epidemiological studies

Author	Case definition for IRIS used
Shelburne et al. (26),(36)	1. Initial response to treatment of previous OI 2. Recurrence of initial symptoms or new symptoms after initiation of ART 3. symptoms or investigations compatible with an inflammatory process 4. Rising CD4 count and falling HIV RNA levels 5. Symptoms could not be explained by a newly acquired infection, by the expected clinical course of a previously recognized infectious agent, or by side effects of therapy.
Breton et al.(30)	1. Reappearance or worsening of previous manifestations or new manifestations despite adequate treatment of OI 2. Disappearance of symptoms after interruption of antiretroviral therapy and recurrence of symptoms after re-initiation of antiretroviral therapy 3. Positive results of bacteriological examination or cultures in organ with suspected OI 4. Histological evidences of inflammation (e.g. granulomatous inflammation in tuberculosis)
French et al (37)	A. <u>Major criteria:</u> 1. Atypical pattern of OIs or tumors in patients responding to ART (exaggerated inflammatory reaction/atypical inflammatory response/localised disease/progression of organ

	dysfunction or enlargement of pre-existing lesions after improvement with specific antimicrobial therapy prior to commencement of ART with exclusion of drug adverse effect or new diagnosis) 2. Decrease in plasma HIV RNA by>1 log10 copies/ml B. <u>Minor criteria</u> 1. Increased CD4 count after ART 2. Increase in immune response specific to pathogen 3. Spontaneous resolution of disease without specific anti-microbial therapy with continuation of ART Diagnosis requires presence of 2 major criteria or the first major criteria with 2 minor criteria
Colebunders et al. (33)	TB IRIS: Case definition 1. Radiological examinations showing worsening or emergence of intra-thoracic lymphadenopathy, pulmonary infiltrates, pleural effusions, abdominal lymph nodes, hepatosplenomegaly 2. A good virological response and/or an increased CD4 lymphocyte count, and/or conversion of Tuberculin skin test(TST) from negative to positive and/or adequate adherence to ART and TB treatment. 3. Clear exclusion of other conditions that could explain the clinical manifestations of the patient, such as TB treatment failure or other concomitant infections, tumours or allergic reaction
Meintjes et al.(35)	Consensus case definition for paradoxical TB associated IRIS (A) Antecedent requirements Both of the two following requirements must be met: • Diagnosis of tuberculosis: the tuberculosis diagnosis was made before starting ART and this should fulfil WHO

	criteria for diagnosis of smear-positive pulmonary tuberculosis, smear-negative pulmonary tuberculosis, or extrapulmonary tuberculosis. • Initial response to tuberculosis treatment: the patients condition should have stabilised or improved on appropriate tuberculosis treatment before ART initiation eg: cessation of night sweats, fevers, cough, weight loss. (this does not apply to patients starting ART within 2 weeks of starting tuberculosis treatment since insufficient time may have elapsed for a clinical response to be reported) (B) Clinical criteria The onset of tuberculosis-associated IRIS manifestations should be within 3 months of ART initiation, reinitiation, or regimen change because of treatment failure. Of the following, at least one major criterion or two minor clinical criteria are required: *Major criteria* • New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement eg, tuberculous arthritis • New or worsening radiological features of tuberculosis (found by chest radiography, abdominal ultrasonography, CT, or MRI) • New or worsening CNS tuberculosis (meningitis or focal neurological deficit) • New or worsening serositis (pleural effusion, ascites, or pericardial effusion) *Minor criteria* • New or worsening constitutional symptoms such as fever, night sweats, or weight loss

	• New or worsening respiratory symptoms such as cough, dyspnoea, or stridor • New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy (C) Alternative explanations for clinical deterioration must be excluded if possible • Failure of tuberculosis treatment because of tuberculosis drug resistance • Poor adherence to tuberculosis treatment • Another OI or neoplasm (it is particularly important to exclude an alternative diagnosis in patients with smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis where the initial tuberculosis diagnosis has not been microbiologically confirmed) • Drug toxicity or reaction Consensus case definition for unmasking TB associated IRIS • Patient is not receiving treatment for tuberculosis when ART is initiated and then presents with active tuberculosis within 3 months of starting ART AND one of the following criteria must be met • Heightened intensity of clinical manifestations, particularly if there is evidence of a marked inflammatory component to the presentation. Examples include tuberculosis lymphadenitis or tuberculosis abscesses with prominent acute inflammatory features, presentation with pulmonary tuberculosis that is complicated by respiratory failure due to adult respiratory distress syndrome, and those who present with a marked systemic inflammatory syndrome related to TB • Once established on TB treatment, a clinical course that is

	complicated by a paradoxical reaction

Significant diagnostic criteria common to all the above definitions are summarised below:

1. Temporal association between starting HAART regimen and subsequent development of clinical phenomena.
2. Clinical picture: Unusual clinical manifestations or unexpected clinical course with an exaggerated inflammatory response.
3. Evidence of preceding immune restoration:
    a. A rise in blood CD4 lymphocyte count.
    b. Preceding fall in HIV viral load.
    c. Restoration of cutaneous hypersensitivity to mycobacterial antigens (PPD or MAC antigen) or increased in-vitro T-cell proliferative responses to PPD or MAC antigen.
    d. Histopathological or cytological appearances of unexpectedly florid cell-mediated immune response within tissue samples.

4. Exclusion of alternative explanations—eg, drug resistance, non-compliance with treatment for the OI, drug reactions

Although most definitions for IRIS exclude patients who have been pre-treated with regimens of ART, there is more awareness now that even patients who have received HAART before and have failed various regimens can develop IRIS with a new regimen. There is a movement to include such cases in the case definition of IRIS (33) . However, being HAART naïve has been identified as one of the risk factors for IRIS and such patients appear to be more at risk than others (26).

Some case definitions have included subsidence of clinical symptoms after interrupting HAART (30). However, this may not be an important part of the case definition as interruption of HAART is not desirable or beneficial.

Risk factors for development of IRIS

The risk factors for IRIS reflect the pathogenesis of this phenomenon. It seems to arise from an interaction between antigen burden, host genetic susceptibility factors and immune dysregulation (37).

Various cohort and retrospective have examined the possible predictors for development of IRIS. The differences in study results may be due to differences and limitations in the methodology. The predictors identified include low baseline CD4 counts(22-25, 38), high baseline viral load (23), increase in CD4 count at one month, younger age(24), low CD4:CD8 ratio(24), increase in CD4:CD8 ratio (30), initiation of ART soon after diagnosis of OI (26), rapid decline in viral load(26, 38) and use of boosted protease inhibitors(38). These studies have been briefly outlined below:

Table 4. Risk factors and predictors of IRIS

Study	Characteristics	Positive predictors	Negative predictors	Non-significant associations
Puthanakit et al (25)	Prospective cohort study	▪ Low baseline CD4 count		▪ Baseline viral load ▪ Viral load decline ▪ Rise in CD4 count
Manabe et al.(38)	Case control study	▪ Boosted protease inhibitor ▪ Nadir CD4 count<100 ▪ Higher baseline viral load ▪ Plasma viral load decline of more than 2.5 logs at time of IRIS	▪ Absolute rise in CD4 count	
Jevtovic et al (22)	Retrospective cohort study (n=389)	▪ CD4<100	A rise in CD4 count above 400 at 4-6 months	▪ CD4 count rise ▪ Viral load decline ▪ Previous OIs
Shelburne et al (26)	Retrospective chart review; HIV, M.Tb, MAC & Cryptococcus neoformans co-infected patients (n=180)	▪ Initiation of ART close to diagnosis of OI ▪ Rapid decline of viral load after HAART initiation ▪ Male gender		▪ Age ▪ Race ▪ Baseline CD4 count ▪ Baseline viral load ▪ PI containing regimens vs other regimens ▪ Duration between

				OI and HAART
French et al (23)	Retrospective study: HIV infected patients commencing HAART ;only responders included(n=132)	▪ Low baseline CD4 counts ▪ High baseline viral load		▪ Rise in CD4 count ▪ Decline in viral load ▪ Duration between OI and HAART
Kumarasamy et al (28)	Prospective cohort: HIV and TB co-infected patients			▪ Baseline CD4 ▪ Rise of CD4 count ▪ Duration between treatment for TB and initiation of HAART
Breton et al (30)	Retrospective cohort: ART naïve HIV and TB co-infected patients	▪ Increase in CD4 count ▪ Increase in CD4:CD8 ratio at one month ▪ Disseminated tuberculosis		
Lortholary (32)	Retrospective multi-centre study: HIV and Cryptococcus co-infected patients initiated on HAART (n=120)	▪ HAART initiated within 60 days of diagnosis of cryptoccal infection ▪ Disseminated cryptococcosis ▪ Fungemia at diagnosis ▪ Lack of CSF sterilisation after two weeks of treatment		▪ Gender ▪ Age ▪ Baseline CD4 counts ▪ Baseline viral load
De Boer et al(39)	Case control study (n=34)	▪ Rise in CD4 counts		▪ CD4:CD8 ratio ▪ Viral load ▪ No. of CDC events prior to HAART initiation
Navas et al (31)	Retrospective study: HIV and TB co-infected patients (n=17)	▪ Early initiation of ART after ATT ▪ Better virological		

		response		
Narita et al (7)	Prospective cohort gp1 HIV+TB initiated on ART (n=33)	▪ Larger drop in viral load after initiation of HAART		▪ Initial CD4 count ▪ Initial CD4 percentage ▪ Initial CD4:CD8 ratio ▪ Initial viral load ▪ Increment in CD4 count
Ratnam et al(24)	Retrospective study of patients initiating HAART	▪ Younger age ▪ CD4 percentage< 10% ▪ CD4:CD8 ratio<0.15		▪ Magnitude of increase in CD4 count over 24wks
Lawn et al.(40)	Retrospective study of patients receiving anti-TB treatment initiated on ART (South Africa)	▪ Low CD4 count ▪ Early initiation of ART after initiation of TB treatment		

In summary, the following risk factors for IRIS were identified:

1. Low baseline CD4 count (22, 23, 25, 38, 40) or percentage (24).
2. Larger rise in CD4 counts (30, 39)
3. High baseline viral load (23)
4. Rapid decline in viral load (7, 26, 31, 38)
5. Early initiation of HAART after OI (26, 31, 32, 40)
6. Disseminated tuberculosis (30, 32)
7. Disseminated cryptococcosis (32)
8. Male gender (26)
9. Younger age (24)
10. Boosted protease inhibitor use (38)

Pathogenesis of IRIS

Although IRIS is a well described phenomenon during immune recovery, the pathogenesis for IRIS remains unclear. It appears to be the composite of interaction of several factors including pathogen load, the rate and magnitude of immune recovery as well as genetic factors.

Antigenic stimulus appears to be essential for the development of IRIS. This is indicated by studies which demonstrated that disseminated tuberculosis and disseminated cryptococcosis are risk factors for development of IRIS indicating that high pathogenic burden may contribute to development of IRIS (30, 32). Antigenic stimulus may be infectious or noninfectious; it may be intact or dead organisms. In noninfectious causes of IRIS, autoimmunity to innate antigens plays a likely role in the syndrome.

The theory that the probability of IRIS depends on the rate and degree of immune reconstitution has received attention. There is evidence for quantitative as well as qualitative restoration of immunity in the first few weeks following initiation of HAART.

Investigators have examined the association between CD4 cell counts and viral loads and the risk of IRIS. Several studies have demonstrated a greater magnitude of rise in CD4 cells among patients with IRIS in comparison with those who did not develop IRIS (30, 39).

IRIS seems to be associated with a restitution of antigen specific response. This has been demonstrated by restoration of delayed tuberculin responses in several studies(1),(23). Initiation of HAART is associated with an increase in CD4 memory cells. Autran et al demonstrated a three-phase T cell reconstitution was demonstrated after HAART, with: (i) an early rise of memory $CD4^+$ cells, (ii) a reduction in T cell activation correlated to the decreasing retroviral activity and (iii) a late rise of "naïve" $CD4^+$ lymphocytes while $CD8^+$ cells declined(41). There appears to be an initial and abrupt increase in the CD45RO subset of CD4 T cells (memory cells), followed over many months by a more subtle increase in the CD45RA subset (naïve T cells). Suppression of viral replication reduces the intense immune activation in lymph node tissues that had previously sequestered lymphocytes in tissue site. The increase in CD4+ T cells following therapy most likely is a combination of initial redistribution from lymph nodes into blood where previously activated lymphocytes were sequestered, accompanied by a continuous slow repopulation with newly produced naive T-cells(42, 43). Cytokines may also have a role in the development of IRIS. Increased levels of interleukin-6 (IL-6)

in IRIS patients(44) may explain the exuberant Th1 response to mycobacterial antigens in subjects with clinical IRIS (27).

Another pathogenic mechanism for IRIS involves host genetic susceptibility to an exuberant immune response to the infectious or noninfectious antigenic stimulus upon immune restoration. Although evidence is limited, carriage of specific HLA alleles suggest associations with the development of IRIS and specific pathogens. Carriage of HLA-A2, -B44 was associated with a history of CMV retinitis and/or encephalomyelitis as IRIS, but not with mycobacterial and other infections (45).

Disease specific manifestations of IRIS:

As IRIS is a pleomorphic phenomenon, the epidemiology, clinical features, and treatment options for the common infectious manifestations of specific IRIS are reviewed below:

Mycobacterial IRIS:

Epidemiology:

The incidence of TB IRIS varies between 37 and 47% in HIV and TB coinfected patients initiated on ART (22, 26, 27, 30, 46). In developing countries, TB-IRIS probably represents upto one-third of all cases of IRIS (46). The high rates of TB-IRIS may be due to persistence of mycobacterial organisms and their cell wall components in host tissues for weeks after initiation of anti-mycobacterial treatment. Even non-HIV infected patients are well known to have paradoxical reactions in TB lymphadenitis, miliary tuberculosis

and CNS tuberculosis (47-51). The high background incidence of paradoxical reactions in TB may be another reason for the greater frequency of TB-IRIS(7).

It is unclear whether early initiation of ART following the initiation of TB treatment is a risk factor for TB IRIS. While some investigators have found early initiation of HAART following initiation of treatment for TB to be a risk factor for IRIS (30, 31), others have not found a significant association (26, 28). In most studies, TB-IRIS occurs within two months of ART initiation (7). Some other studies have shown that low CD4 count, a good immunological and virological response to ART and disseminated TB are also risk factors for development of IRIS (7, 26, 30, 31, 46). However, others such as Kumaraswamy et al reported no difference between baseline CD4 counts, rise in CD4 counts and duration between treatment for tuberculosis and HAART between patients with and without IRIS (28).

The return of infection specific immunity in the form of tuberculin responses has been consistently demonstrated in various studies (23).

In most studies, TB IRIS seems to be most common among patients intitiated on ART within the first two months. Several authors have suggested delaying treatment with ART until after two months of treatment with anti-tuberculous therapy (ATT). However, in a decision analysis on a hypothetical cohort of 1000 patients studying mortality in three groups of patients (group 1: ART initiated within first two months of ATT, group 2: ART deferred to between 2 and 6 months of ATT and group 3: ART after completion of ATT), mortality was the lowest in the group initiated on ART earliest regardless of IRIS.

Deferred HAART was favored over early HAART only if the IRIS-related mortality rate in the early group exceeded 4.6%. These results support early initiation of HAART in patients with AIDS, except when IRIS-related mortality rates are high(52).

One study suggested that median time to onset of IRIS in central nervous system (CNS) TB is longer than other sites of TB IRIS (53).

Clinical features:

The most commonly reported manifestations of *M tuberculosis*-associated IRIS were fever, lymphadenopathy, and worsening respiratory symptoms. In one study, lymphadenopathy was the most frequent manifestation, occurring in 71% of the patients (54). The second most common manifestation was the development or deterioration of parenchymal lung disease as seen in 28% patients. Worsening parynchymal lung infiltrates have been commonly reported in various studies on IRIS (7, 28, 30, 46, 55). Other miscellaneous manifestations include hepatosplenomegaly, pleural effusion, ascites, psoas abscess, splenic abscess, other intra-abdominal abscesses, disease of the caecum with or without perforation, epididymo-orchitis, central nervous system lesions, skin lesions, ureteric compression, acute renal failure(8), and hypercalcaemia (46, 54)

Treatment:

Treatment of TB IRIS depends on organs involved and severity. Non-serious manifestations respond to initiation of ATT. Steroids have been tried for seriously ill patients. Use of steroids has ranged from intravenous methylprednisolone to lower doses of oral prednisolone. Steroids have been anecdotally effective but there is lack of

controlled trials to demonstrate this. Steroids are indicated in patients with CNS TB. Other indications for steroids remain unclear.

Atypical mycobacterial IRIS:

Epidemiology:

Atypical mycobacterial IRIS is known to occur with immune reconstitution (1, 2, 56-60). It was first described with zidovudine therapy but has been described in patients on protease inhibitor regimens following this(1). Of all atypical mycobacteria (table 1), *Mycobacterium avium intracellulare* appears to be the commonest. Non-TB mycobacterial IRIS also seems to be associated with specific reconstitution of CD4 memory cells which can be demonstrated by immunophenotyping studies of lymph nodes (2).

Clinical features:

MAC associated IRIS has varied manifestations. These include focal lymphadenitis (1, 23, 57), pyomyositis (56), soft tissue abscesses, acute respiratory distress syndrome (ARDS) (59), endobronchial lesions(59), osteomyelitis (59, 60), peritonitis(59), intraabdominal abscesses, intestinal obstruction (59) and adrenal masses(59). Most patients developed manifestations between 1-8wks(1, 56-59). One study however described late non-mycobacterial IRIS in the form of osteomyelitis occurring after more than 10 months of ART (60).

Treatment

Antimycobacterial chemotherapy along with surgical excision of lymph nodes has been used in some studies. However, this may result in non-healing sinuses. Needle aspiration has also been tried in some cases. In severe cases steroids have been tried with variable response.

Hepatitis C

There are several reports of IRIS related to Hepatitis C infection (HCV). In one study involving a retrospective cohort of responders to HAART, three patients had hepatitis of which only one had been known to have hepatitis C infection previously. The other two seroconverted following initiation of HAART suggesting that the hepatitis resulted from the restoration of an immune response against HCV. Subsequent analysis of stored plasma showed that HCV RNA had been present even prior to initiation of HAART. Both these patients had evidence of chronic hepatitis without eosinophilia or granulomata in a liver biopsy indicating that hepatitis was not drug induced (23). HCV IRIS in this study occurred at a mean of 12 weeks after initiation of HAART.

Cutaneous IRIS

a) Dermatomal Zoster

Incidence of herpes zoster IRIS have varied from 6-40% (13, 22-24, 61). Most patients have a CD4 count of less than 50 cells/ml at baseline. This is thought to be a late occurring IRIS, sometimes occurring 30 weeks after commencing anti-retroviral therapy and almost never occurring in the first four weeks(13). In one case control study among

patients with HIV who developed herpes zoster, being on HAART increased the odds of developing herpes zoster by two to five times (62). Herpes zoster IRIS may be associated with complications including post herpetic neuralgia, infection, ocular and neurological complications.

Treatment:

Treatment with seven days of acyclovir appears to be effective in treatment of herpes Zoster IRIS. Addition of steroids to treatment with acyclovir was studied in a randomised controlled trial. Addition of steroid decreased healing times, improved acute pain, and quality of life, but did not affect the incidence or duration of postherpetic neuralgia (63). Sorivudine has been studied in comparison with acyclovir and can be used as an alternative(64). Opiods, tricyclic agents and gabapentin can be used for control of post-herpetic neuralgia.

b) Lepra reactions:

There are several case reports of reversal reactions described in patients initiated on HAART. This may be the first presentation of Hansen's disease (65-67). The patients are usually in the borderline tuberculoid or tuberculoid spectrum. Skin biopsy typically shows well formed granulomas. This is usually associated with a rise in CD4 counts. Time of occurrence is usually between one and six months after initiation of HAART (65). The lepromin test may or may not be positive. Type 1 reactions are usually associated with increase in cellular immunity and are not very common in patients with HIV infection. Reactional leprosy type 1 can be considered a marker of IRIS in HIV-

infected patients who are receiving HAART. Treatment for IRIS presenting as a lepra reaction is the same as for type I reaction in Hansen's disease.

c) Molluscum Contagiosum

There are several case reports of patients developing molluscum contagiosum as IRIS (23, 26). In one study, 9% (4/44) of patients developed molluscum contagiosum following initiation of HAART. The median time to development of IRIS was 8 weeks(24).

Cryptococcal meningitis

The incidence of IRIS in patients with HIV and crypococcal meningitis newly initiated on ART was reported to be 30% in one cohort study (68).

Clinical features:

Various manifestations of cryptococcosis as an IRIS have been described in patients initiated on ART including cryptococcal meningitis, raised intra-cranial pressure, intrathoracic lymphadenopathy, hypercalcemia, cavitatory pneumonia(15, 36), ARDS (36) and supraclavicular abscess(15). IRIS usually occurs within the first two months (14, 36, 69, 70) although some studies indicate that it can occur as late as 11 months after initiation of ART(15). Although cryptococcal infection in HIV may be characterised by a low grade inflammatory response causing only mild CSF leukocytosis, in IRIS it is usually associated with a marked inflammatory cellular response with negative smears and cultures (36, 69). Since relapse is common in treated cryptococcal meningitis, it is

important to distinguish this from immune reconstitution (70). In one study, high antigen titres in CSF and early initiation of ART following treatment for cryptococcal meningitis (<30days) were found to be risk factors for IRIS (68). *C. neoformans*-related IRIS patients also had higher baseline plasma HIV RNA levels and higher CSF cryptococcal antigen titers, opening pressures, WBC counts, and glucose levels (68, 71).

Treatment:

Amphotericin and flucytosine combinations are associated with the fastest clearance of infection in cryptococcal meningitis (72). In severe IRIS, steroids have been used and have been found to be useful in case reports (36, 73). Hydroxychloroquine has also been used in some cases for its anti-inflammatory activity (73)

CMV IRIS:

CMV IRIS was described when CMV retinitis was noticed to occur in patients on HAART with CD4 counts that were much higher than expected. This was noticed to occur 4-7weeks after initiation of HAART (10). In a retrospective cohort, CMV-related IRIS was common (6/33 of IRIS cases, or 18%) (23). A new syndrome of immune recovery vitritis (IRV) was described as a syndrome of posterior segment intraocular inflammation that causes visual loss in patients with AIDS and CMV retinitis. On analysis of data from the pre-HAART era, this syndrome was noted to occur only in patients on HAART who had CMV retinitis in the past. It was associated with marked inflammation, visual impairment and higher CD4 counts (74). Immune recovery uveitis presents presents as vitritis, macular edema, or formation of epiretinal membrane and can severely compromise vision. This is thought to be an inflammatory response to persisting

CMV antigen and not due to the replication of the virus. In one study, PCR for CMV from aqueous humor was negative in all patients with IRV and they had high levels of IL-12 and low levels of IL-6 and interferon gamma (suggestive of an antigen specific response) (75). The incidence of IRV varies between 17.6% to 63% among patients with previous CMV retinitis in different studies (76, 77). In one study, the median time to development of IRV was 43 weeks (76). Male gender, use of ART, higher CD4 cell counts, and involvement of the posterior retinal pole are associated with a reduced risk of developing IRV, whereas prior use of intravitreous injections of cidofovir, large retinal lesions, and adequate immune recovery on ART are associated with increased risk of IRV (77).

Treatment:

Treatment of IRIS associated CMV retinitis and IRV may involve anti-CMV therapy with gancyclovir or valgancyclovir(78). However, the usefulness of this is debatable since immune recovery vitritis is not considered an infective complication as evidenced by negative CMV DNA tests in all these patients. Furthermore, ongoing treatment of healed CMV retinitis after immune recovery does not appear to protect against the development of immune recovery uveitis (79). In fact cidofovir use has been associated with a higher incidence of immune recovery uveitis (79). The use of systemic corticosteroids has been successful, and IRV may require periocular corticosteroid injections (80-82).

Methodology

Type of study

Prospective cohort study of HIV infected patients initiated on HAART at our hospital or referred to ART centres between 1st November 2006 and 1st November 2007.

Sample size

With an expected incidence of 25% and absolute precision of 8% with an alpha error of 5% and expected loss to follow up taken as 20%, the desired sample size to calculate incidence is 142.

Methods

All patients initiated on HAART or referred for HAART to ART centres, on follow up at our hospital between 1st November 2006 and 1st November 2007 were recruited. Patients had baseline CD4 lymphocyte counts tested prior to initiation of HAART. A complete physical examination of every patient was done at baseline. Clinical and laboratory characteristics, age, WHO staging of HIV infection, body mass index (BMI), previous opportunistic infections, CD4 lymphocyte counts and absolute lymphocyte counts (ALC) were recorded. Patients were monitored for development of new symptoms or

opportunistic infections for a period of six months. Patients who did not return to the clinic on follow up dates were contacted by phone and mail. Any new symptoms were recorded and a physical examination was carried out at every visit.

The following definitions were used to diagnose IRIS and IRIS like syndrome:

Definition of typical IRIS (Immune reconstitution inflammatory syndrome)

Typical IRIS meets the following criteria

- HIV infected person receiving HAART deteriorating following initiation of HAART
- Immune reconstitution evidenced by

  Decrease in HIV-1 RNA levels from baseline or

  Increase in CD4 counts from baseline
- Clinical symptoms, signs or laboratory investigations consistent with an inflammatory process
- Clinical course not consistent with
  1. Expected course of previously diagnosed OI or expected course of newly diagnosed OI
  2. Drug toxicity

Definition of IRIS like syndrome

- Onset of new OI after initiation of HAART
- Worsening of old OI after initiation of HAART
- Worsening not due to drug toxicity or irregular treatment for previous OI
- On treatment with regular HAART

Incidence of IRIS was calculated in the cohort using the above definitions. Incidence rates of IRIS among patients with pre-existing opportunistic infections receiving HAART were calculated for each opportunistic infection.

Patients with any new clinical symptoms underwent physical examination and CD4 lymphocyte counts were enumerated. Clinical symptoms, signs, relevant investigations, CD4 lymphocyte counts, time from previous opportunistic infection, treatment and outcomes were recorded in detail. Type of OI associated with IRIS was determined according to criteria described below. Baseline characteristics of patients who developed IRIS were compared with those of patients who did not, and predictive factors were identified.

Definitions of specific IRIS:

Mycobacterial IRIS:

TB lymphadenitis associated IRIS:

Enlarging lymph nodes following initiation of HAART in patients known to have previous tuberculous lymphadenitis (confirmed by previous smear or culture) or enlarging lymph nodes following intiation of HAART with smear or culture positivity among patients with no previous diagnosis of TB lymphadenitis.

Pulmonary tuberculosis associated IRIS:

Appearance of fever with, or without cough and breathlessness, with, or without chest infiltrates following initiation of HAART in patients known to have tuberculosis (or) appearance of fever with or without cough, breathlessness and chest infiltrates in patients not known to have TB, confirmed by sputum acid fast bacilli (AFB) smear positivity or culture positivity

Disseminated tuberculosis

Appearance of fever with or without hepatosplenomegaly and lymphadenopathy with isolation of AFB on smear or culture from bone marrow, lymph node , liver biopsy or cerebrospinal fluid (CSF) or histopathological confirmation by granuloma formation in bone marrow or liver.

Tuberculous meningitis

Appearance or worsening of symptoms of fever and headache with or without altered sensorium and neck rigidity with elevated protein and cellular response in CSF with lymphocytic predominance, cultures and smear for cryptococcus being negative, with or without CSF AFB smear or culture isolation with response to treatment with ATT and steroids.

Cryptococcal IRIS

Cryptococcal meningitis associated IRIS

Appearance or worsening of fever and headache with or without altered sensorium and neck rigidity with CSF positive for cryptococcus India ink, cryptococcal antigen or cryptococcal culture.

Pneumocystis jirovecii associated IRIS

Worsening breathlessness, fever and hypoxemia with bilateral interstitial lung infiltrates or nodular shadows following initiation of HAART which improves on treatment with HAART and cotrimoxazole or sputum positive for Pneumocystis jirovecci by fluorescent antibody or silver staining.

Cytomegalovirus (CMV) associated IRIS

Blindness or diminished vision with fundoscopic appearance suggestive of CMV retinitis or features suggestive of CMV vitritis or uveitis. Features of gastrointestinal involvement with confirmation by histopathology or virology to suggest CMV colitis or oesophagitis.

Progressive multifocal leukoencephalopathy (PMLE) IRIS

Appearance of focal neurological deficits with imaging suggestive of white matter inflammation.

Toxoplasma IRIS

Appearance of focal neurological deficits with imaging showing a ring enhancing lesion with response to treatment for toxoplasmosis alone.

Hansen's disease IRIS

Swelling, erythema or tenderness of patches in patients with leprosy or neuritis suggesting a type I lepra reaction.

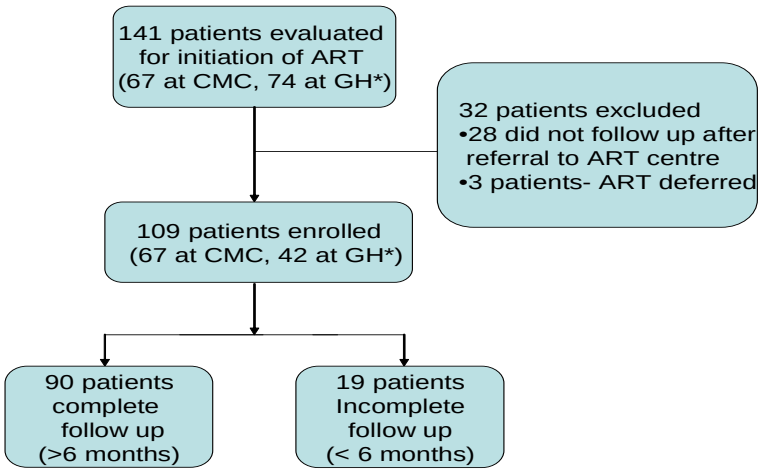
Statistical analysis:

Means of continuous variables were compared using the independent sample T test among patients who did and did not develop IRIS. Discrete variables were compared using chi square test. Analysis was done with SPSS version 11.

Results

A total of 141 patients were evaluated for initiation of HAART between 1st November 2006 and 30th October 2007 (Figure 1). Of these, 109 were initiated on HAART (67 at Christian Medical College and 42 at different other ART centres including four centres in Tamil Nadu and three centres in Andhra Pradesh). These 109 patients were followed up for a total of 62 person-years and a mean duration of 207 days. For 19 patients (17%) the follow-up was less than six months ranging between 14 and 136 days. Ten of these patients were followed up at CMC and 9 were followed up at government-run ART centres. Of the 90 patients who completed six-months follow-up, 75 (83%) patients were followed up in person at the Infectious Disease Clinic at CMC and the remainder through phone and mail.

Figure 1. Patient recruitment for study



*GH Government hospital ART centres

Table 5. Baseline characteristics of patients

Baseline characteristics	All patients n=109
Sex	
Male	72 (66%)
Female	37 (34%)
Age (mean in yrs)	38 (range 23-76)
BMI (mean)	21 (range 11-28)
BMI subgroups [%] (n=101)	
<18	28(28%)
18-25	57(57%)
>25	16(15%)
WHO stage	
I	37 (34%)
II	8(7%)
III	19(18%)
IV	45 (41%)
Mean CD4 counts (cells/ml)	131 (range 7-346)
CD4 count subgroups	
<50	18(17%)
50-100	24(23%)
100-150	18(17%)
150-200	23(22%)
>200	21(20%)
Mean Absolute lymphocyte count(/ul)	1358 (range 44-4459)
HAART regimens (n=101)	
D4T+3TC+NVP	36(37%)
ZDV+3TC+NVP	32(33%)
D4T+3TC+EFV	17(17%)
D4T+3TC+EFV	8(8%)
EMT+TDF+EFV	5(5%)

D4T : Stavudine
3TC : Lamivudine
ZDV: Zidovudine
NVP: Nevirapine
EFV: Efavirenz
TDF: Tenofovir
EMT: Emtricitabine

Table 6: Previous opportunistic infections in cohort (n=109)

PRESENCE OF PRIOR OPPORTUNISTIC INFECTION	
Previous Opportunistic Infections (OIs)	Entire group No.(%) n=109
Presence of prior opportunistic infections	49(45%)
Absence of prior opportunistic infection	60(55%)
INDIVIDUAL OPPORTUNISTIC INFECTIONS	
TB (all)	40(35%)
Pulmonary TB	5
TB lymphadenitis	13
Pleural effusion	2
Pericardial effusion	1
Disseminated TB	15
TB Meningitis	2
Bone TB	2
Cryptococcal meningitis	0(0%)
Pneumocystis Pneumonia (PCP)	2(2%)
Cytomegalovirus Infection (CMV)	2(2%)
Herpes zoster	2(2%)
Candidal esophagitis	2(2%)
Chronic diarrhea	2(2%)

Baseline characteristics:

The baseline characteristics of the patients are presented in Table 5 (on opposite sheet). Of all patients, 66% of patients were male and 59% of the patients were in WHO stage III and IV HIV infection at the time of enrollment. BMI was less than 18 in 28% of patients. Mean CD4 lymphocyte count was 131 cells/ml and 79% patients had CD4 lymphocyte counts below 200 cells/ml, indicating that the majority of patients had AIDS. Of all patients, 68% were on treatment with nevirapine-based regimens (Table 5). The remaining patients were on various combinations of efavirenz-based regimens. None of the patients were on protease inhibitors.

Among the patients, 45% had a previous OI, the commonest being TB (40 of 49 patients). Of these 40 patients with TB, 15 (37.5%) had disseminated tuberculosis, 13 (33%) had previous tuberculous lymphadenitis, 2 (5%) had pleural tuberculosis, 2 (5%) had TB meningitis and 2 (5%) had TB osteomyelitis. Only one patient had previous pericardial TB. Two patients had previous Pneumocystis pneumonia (PCP), Cytomegalovirus (CMV) retinitis, herpes zoster and esophageal candidiasis. There were no patients with cryptococcal meningitis in the cohort. The details of previous opportunistic infections in the study group are presented in table 6 (on opposite sheet).

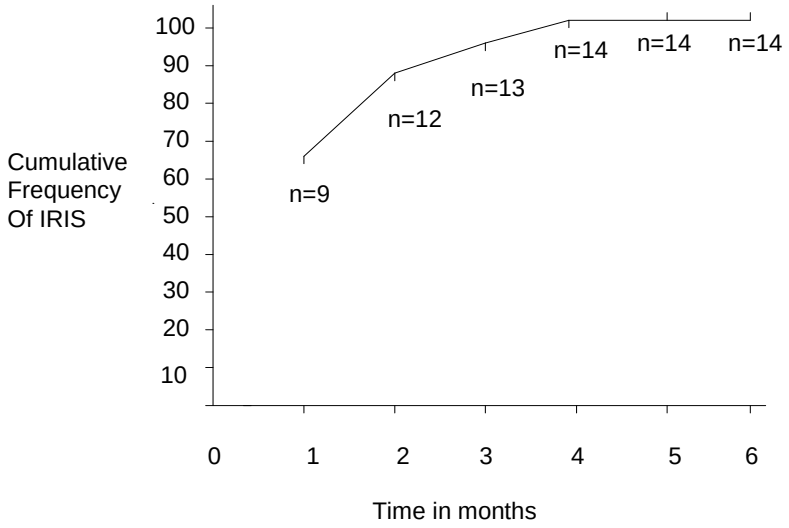
Table 7: Overall incidence of IRIS and opportunistic infection specific IRIS incidences:

Type of IRIS	No.	Incidence	Confidence limits
All IRIS	14	12.8%	(7.2%, 20.6%)
Tuberculous IRIS	9	8%	(3.8%,15.1%)
CMV IRIS*	2	1.8%	(0.2%, 6.5%)
Cryptococcal IRIS	1	1%	(0.02%,6.4%)
PMLE**	1	1%	(0.02%,6.4%)
Herpes Zoster	1	1%	(0.02%,6.4%)

*Cytomegalovirus immune reconstitution inflammatory syndrome

**Progressive multifocal leukoencephalopathy

Figure 2: Cumulative frequency of IRIS by time



Incidence of IRIS:

A total of 14 patients developed IRIS out of 109 patients, with an incidence of 12.8% (CI 7.2%, 20.6%). Cumulative incidence was 22 per 100 person-years. Cumulative incidence in the first two months after initiation of HAART was 11.4% (12 of 109 patients). Incidence of IRIS after first two months was only 1.4% (2 of 109 patients) (see Figure 2). Among various types of opportunistic infections presenting as IRIS, TB IRIS was the commonest with an incidence of 8% (CI 3.8%, 15.1%). The incidence of disease specific IRIS is outlined in Table 7:

The frequency of TB IRIS among patients with patients with prior TB was 12.5% (4.2%, 26.8%). The same frequency could not be calculated for other opportunistic infections because of the small numbers.

Table 8: Profile of IRIS

Type of IRIS	No.	Prior infection with same OI	Mean CD4 at time of initiation of HAART(/ul)	Mean CD4 at time of IRIS(/ul)	Mean time to IRIS (days)	Management	Outcome
All TB IRIS	9	5	123	419	43	ATT*	Improved
Types of TB							
Disseminated	1		134	272	35	ATT	Improved
Lymph node	3		162	418	79	ATT	Improved
CNS	2		140	818	14	ATT+st**	Improved
Skin	1		154	418	30	ATT	Improved
Pulm TB	2		161	162	5	ATT	Improved
All CMV IRIS	2	0	24	146	27	Gancyclovir	Improved
Individual CMV infection						-	
CMV Retinitis	1		7	161	39		Improved
CMV Esophagitis	1		42	131	15		Improved
Herpes zoster	1	0	177	626	27	Acyclovir	Improved
Cryptococcal meningitis	1	0	119	NA	7	Amphotericin	Expired
PMLE	1	0	116	151	4	-	Improved
Total (All IRIS)	14	5	121	332	33		

*ATT : Anti-tuberculous treatment
**st: Steroids

Table 9: Magnitude of rise in CD4 lymphocyte counts in patients with IRIS

Magnitude of rise in CD4 lymphocyte counts	No. total n=12
< 100 cells/ml	4
100 – 200 cells/ml	3
200 – 400 cells/ml	3
>400 cells/ml	2

Profile of IRIS patients:

Overall profile of IRIS

The profile of IRIS patients is described in table 8.

There were 14 cases of typical IRIS and 3 cases of IRIS like syndrome. The three cases of IRIS like syndrome were not included in the final analysis. Of the cases of IRIS, there were 9 cases of TB IRIS, 2 CMV IRIS, 1 herpes zoster IRIS, 1 cryptococcal meningitis IRIS and 1 PMLE IRIS. Thirteen of 14 patients presented with AIDS defining illnesses. There were no cases of Pneumocystis jirovecii or atypical mycobacterial IRIS. Only 5 of the fourteen cases had a prior opportunistic infection, all in the TB IRIS group. The mean CD4 at the time of initiation of ART was 121 cells/ml and only 2 patients had a baseline CD4 count of more than 200 cells/ml. The mean CD4 lymphocyte count at the time of development of IRIS was 332 cells/ml. All patients had an increase in CD4 lymphocyte count, but the degree of increase was variable from less than 100 cells/ml to more than 400 cells/ml (Table 9). The time to development of IRIS following initiation of HAART was variable (4-120 days) with a mean of 33 days. 85% of patients developed IRIS within two months of initiation of HAART. None of the patients had more than one opportunistic infection presenting as IRIS. There was a variable rise in CD4 counts in cases of IRIS (Table 9).

Table 10: Proportion of patients who fit specific definition criteria for IRIS:

Defainition criteria for IRIS	Proportion of patients fitting criteria no.(%)
• HIV positive receiving HAART developing deterioration following initiation of HAART	14(100%)
• Immune reconstitution evidenced by Decrease in HIV-1 RNA levels from baseline or Increase in CD4 counts from baseline	12(85%)
• Clinical symptoms, signs or investigations consistent with an inflammatory process	14(100%)
• Clinical course not consistent with • Expected course of previously diagnosed OI or expected course of newly diagnosed OI • Drug toxicity	13(92%)

Of the 14 patients, all cases fulfilled criteria of deterioration following initiation of HAART and clinical profile suggestive of an inflammatory process (Table 9). Twelve patients had evidence of immune reconstitution and 13 had a clinical course not consistent with previous or newly diagnosed opportunistic infections. The proportion of patients that satisfied individual criteria for IRIS are shown in table 9.

All patients were treated for underlying opportunistic infections and two required treatment with steroids. All cases improved on treatment of OI, except one, who expired due to drug toxicity (case M, Appendix). HAART was not withdrawn for any patient.

Profile of TB IRIS (see appendix for individual case descriptions- cases A to I)

The most common opportunistic infection manifesting as IRIS was tuberculosis in 64% of cases. Of 9 patients with tuberculosis, 3 presented with TB lymphadenitis, 2 with TB meningitis, 2 with pulmonary TB, 1 with a tuberculous ulcer over the right thigh and one with disseminated tuberculosis. Only five of the patients had evidence of prior TB. The time to development of TB IRIS following initiation of HAART varied from 5 days to 120 days. Two patients who went on to develop IRIS had been suspected to have tuberculosis prior to initiation of HAART but were not treated. In one of these patients, the diagnosis could not be confirmed and in another empirical anti-tuberculous therapy was discontinued due to drug rash. The clinical severity of TB IRIS varied from localized lymph nodal involvement to severe disseminated involvement with high fever, pulmonary, disseminated lymph node and hepatic involvement. In two cases the site of TB IRIS involvement was not the initial site of TB involvement. Five of 9 patients

had acute presentations (<2weeks). TB IRIS occurred in all groups irrespective of time of initiation of HAART in relation to TB treatment; 2 cases initiated on HAART within 2 months of TB treatment and 3 cases after completion of TB treatment.

All patients who presented with localised TB lymphadenitis had involvement of only one group of lymph nodes with demonstration of granulomatous inflammation on fine needle aspiration cytology. Both patients with CNS tuberculosis presented with paradoxical worsening after initial improvement on anti-tuberculous treatment and demonstrated cellular response in CSF. Both patients with pulmonary involvement presented acutely with lower zone involvement and sputum AFB positivity. The patient with skin involvement presented with ulcerated lesion of the thigh. Four patients had multi-organ involvement at the time of presentation. These patients had combinations of pulmonary, hepatic, CNS and lymph node involvement. Of these, three patients had marked alkaline phosphatase elevation and in one, granulomatous inflammation was demonstrated on liver biopsy.

All patients improved on treatment for tuberculosis. Both patients with CNS tuberculosis were also treated with steroids.

Profile of CMV IRIS (see appendix for individual case descriptions- cases J and K)

There were two patients who developed CMV related IRIS. One patient presented with retinal involvement and the other with oesophageal and retinal involvement. Their baseline CD4 counts were 7 cells/ml and 42 cells/ml respectively. Neither of these patients had previously detected CMV. The time to development of IRIS was 11 days and 14 days in case J and K respectively. CD4 counts rose by 154 and 89 cells/ml in case J and K respectively.

Case K developed worsening dysphagia and choking following intitiation of HAART and was found to have oesophageal ulceration with a tracheo-oesophageal fistula. Fundus examination showed peripheral CMV retinitis and peripheral blood CMV PCR was positive. Although CMV oesophagitis could not be confirmed on the oesophageal biopsy), CMV was the most likely etiology in view of concurrently occurring CMV retinitis. The second patient developed CMV retinitis with loss of vision following initiation of HAART with partial improvement on treatment with gancyclovir.

Herpes Zoster IRIS (see appendix for individual case description- case L)

One patient developed localized dermatomal herpes zoster accompanied by severe pain 27 days after initiating HAART. His CD4 count rose to 626 cells/ml from 177 cells/ml at baseline. He improved on treatment with acyclovir and did not develop post herpetic neuralgia subsequently.

Crytpococcal meningitis IRIS (see appendix for case descriptions- case M)

One patient presented with cryptococcal meningitis three months following initiation of HAART. His baseline CD4 count was 119 cells/ml. He had acute deterioration with a cellular response in CSF and india ink positivity consistent with a diagnosis of cryptococcal IRIS. He had not been diagnosed to have cryptococcal meningitis prior to this. He developed severe refractory hypokalemia and acute renal failure within a week of initiating amphotericin. The possible cause of death in this patient is drug related toxicity.

PML IRIS (see appendix for case description- case N)

One patient developed PML related IRIS. This patient presented with acutely worsening cerebellar symptoms in the form of dysarthria and ataxia 3 days following initiation of HAART. His CD4 counts demonstrated a rise from 116 cells/ml at baseline to 151 cells/ml at time of IRIS. MRI brain demonstrated cerebellar demyelination consistent with a diagnosis of PML. His condition improved markedly, without treatment with steroids.

Individual case presentations are described in detail in the appendix.

Table 11: Baseline characteristics of 106 patients with and without IRIS (3 patients with IRIS like syndrome excluded)

Baseline characteristics	Patients with IRIS	Patients without IRIS	P value
Total number	14	88	
Sex			
Male	10(71%)	60(66%)	0.65
Female	4(29%)	32(34%)	
Age (mean in yrs)	41	38	0.27
BMI (mean)	20	21	0.24
BMI subgroups [%] (n=101)			
<18	7(50%)	21(24%)	0.12
18-25	5(35%)	52(59%)	
>25	2(14%)	14(16%)	
WHO stage			
I	4(28%)	33(36%)	0.20
II	0(0)	8(8%)	
III	2(14%)	15(16%)	
IV	8(57%)	36(39%)	
Mean CD4 counts (cells/ml)	121	134	0.59
CD4 count subgroups			
<50	4(29%)	14(16%)	0.32
50-100	1(7%)	23(25%)	
100-150	2(14%)	16(18%)	
150-200	5(36%)	18(20%)	
>200	2(14%)	19(21%)	
Mean Absolute lymphocyte count(cells/ml)	1170	1398	0.34
HAART regimens (n=98)			
D4T+3TC+NVP	5(35%)	31(37%)	NA
ZDV+3TC+NVP	4(29%)	28(33%)	
D4T+3TC+EFV	1(7%)	16(19%)	
D4T+3TC+EFV	0(0%)	8(10%)	
TDV+EMT+EFV	4(29%)	1(1%)	

Predictive factors for IRIS:

The baseline characteristics and previous opportunistic infections among patients with and without IRIS are outlined in Tables 10 and 11.

Baseline characteristics were compared among patients with and without IRIS. There were no significant differences in age, gender, baseline CD4 counts, absolute lymphocyte counts or mean body mass index (BMI) between the patients who developed IRIS and those who did not (Table 6). Among patients with CD4 counts below 200 cells/ml, 15% developed IRIS as compared to 10% among patients with higher CD4 counts (p=0.55).

Mean BMI was similar among patients with and without IRIS. 25% of the patients with a BMI of less than 18 developed IRIS compared to 12.5% of patients with a BMI of more than 25, although this difference was not significant (p=0.124).

The incidence of IRIS in patients with early stages of HIV infection (WHO stage I and II) was 8.9% compared to 16.4% in patients with late stages of HIV infection (WHO stages III and IV), although this difference was not statistically significant (p=0.25).

Patients with early and late stages of HIV infection developed similar types of IRIS, although CMV infections were more common in WHO Stage III and IV disease. The mean time to development of IRIS was similar in early and late stages of HIV infection.

Table 12: Previous opportunistic infections among patients with and without IRIS

Previous OIs	IRIS*	No IRIS*	P value
No prior OI	5(36%)	55(60%)	0.09
Prior OI	9(64%)	37(40%)	0.09
TB (any)	7(50%)	30(33%)	0.20
Pulm TB Lymphadenitis Pleural Pericardial Disseminated TB Meningitis Bone	2(29%) 1(14%) 0(0%) 0(0%) 2(29%) 2(29%) 0(0%)	2(7%) 10(33%) 2(7%) 1(3%) 13(43%) 0(0%) 2(7%)	NA
Cryptococcal meningitis	0(0%)	0(0%)	NA
PCP	1(7%)	1(1%)	NA
CMV	0(0%)	2(2%)	NA
Herpes zoster	0(0%)	2(2%)	NA
Candidal esophagitis	2(14%)	0(0%)	NA
Chronic diarrhea	0(0%)	2(2%)	NA

*3 patients with doubtful IRIS excluded

There was no significant difference between incidence of IRIS among patients who received efavirenz and nevirapine based regiments (19% and 12% respectively, p=0.32). However, among patients being treated with emtricitabine, tenofovir and efavirenz, four out of five patients (80%) developed IRIS. The mean rise in CD4 lymphocyte count from baseline was 375 cells/ml (range, 1 to 980 cells/ml). Since these numbers are small, it is difficult to comment upon their significance.

Out of the 14 patients who developed IRIS, 9 patients had been previously diagnosed to have an opportunistic infection. Of these 9 patients, only 5 patients developed manifestations of an opportunistic infection similar to their previous opportunistic infection. The incidence of IRIS was higher among patients with previous opportunistic infections although this difference did not attain statistical significance (19.6% among patients with previous opportunistic infections compared to 8.3% among those without previous OIs, p value=0.09). Among patients with previously diagnosed tuberculosis 19% developed IRIS as compared to 10% among patients without previously diagnosed tuberculosis (p=0.20). Disseminated tuberculosis was not found to be a significant predictive factor for development of IRIS (p=0.57).

Early initiation of HAART after diagnosis of opportunistic infection (less than two months) was not found to be a significant predictive factor for IRIS. Among patients with tuberculosis 17% of patients initiated on HAART within two months and 27% of patients initiated on HAART more than six months after initiation of ATT developed IRIS. These differences were not statistically significant.

Multivariate analysis could not be done in relation to the baseline characteristics and previous opportunistic infections due to the low rate of events and lack of significant predictive factors for IRIS on univariate analysis.

Discussion

This study has shown that IRIS is a significant problem in patients started on HAART in India. The calculated incidence of IRIS in the cohort studied was 12.8% (14/109 patients). This is the only prospective study that has studied the overall incidence of IRIS. The overall IRIS rate reported in this study at 12.8% was lower than that reported in other studies of 25%, 16.7% and 22% (22-24). The reasons for lower rates of IRIS in our study may be the following:

1. A smaller proportion of patients with very low CD4 counts in this study: French et al studied a cohort in which 58% of patients had a CD4 count less than 50 cells/ml as opposed to 17% of patients in our cohort suggesting that the patients in the aforementioned group may have had more advanced disease(23). In another study, 61% of patients had CD4 counts below 100 cells/ml(22).
2. The prospective design of this study: Most other studies that reported IRIS rates were retrospective studies that may have over-represented event rates(22-24).
3. Lower rates of dermatological IRIS: In other studies(22-24) the proportion of dermatological IRIS varied from 43 to 78% compared to 7% in our study. The low rates of dermatological IRIS may reflect under-reporting of skin lesions among patients in this study.
4. Lack of use of protease inhibitor (PI) based regimens in this study: Jevtovic et al reported use of PI based regimens in 64% of patients compared to no patients in this study(22).

The variable rates of IRIS in different studies is probably a reflection of the following:

a. The heterogeneous nature of the syndrome due to a variety of opportunistic infections
b. The complex interplay between antigen burden, immune response and underlying genetic factors that underlie the pathophysiology of the syndrome.
c. Multiple factors may determine the occurrence of IRIS such as the background opportunistic infections, severity of immunodeficiency, type of ART and timing of ART.

For all these reasons IRIS may not occur at a predictable rate.

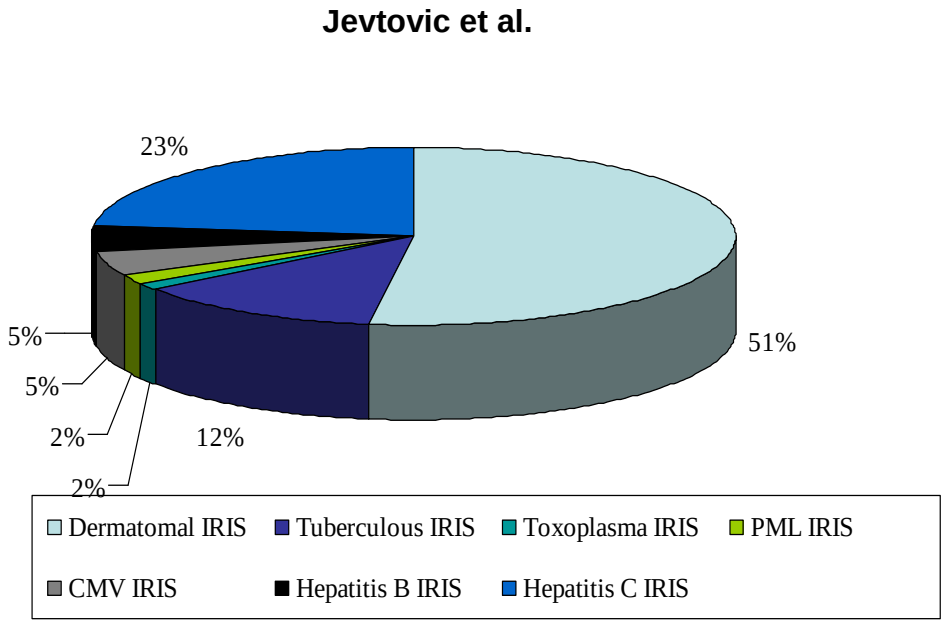
There was a variable rise in CD4 lymphocyte count among patients in this study. Grabar et al. showed that CD4 mean increase during the first 6 months on HAART was 42.9 cells/ml per month in patients under 50 years and 36.9 cells/ml per month in patients over 50 years of age(83). The rise of CD4 in some of our patients far exceeded this anticipated rise in the given time period. Among studies on patients with IRIS, higher increments in CD4 count have been reported. French et al. reported median increase of 97 and 66 cells/ml among patients with and without IRIS at six weeks following initiation of IRIS (23). Breton et al. also described an increment in CD4 count of 99 cells/ml in patients with IRIS in comparison to 35 cells/ml in patients without IRIS at one month following inititation of HAART (30). The mean rise in CD4 count at time of IRIS from baseline in this study was 111 cells/ml, which is consistent with the data in the studies described above.

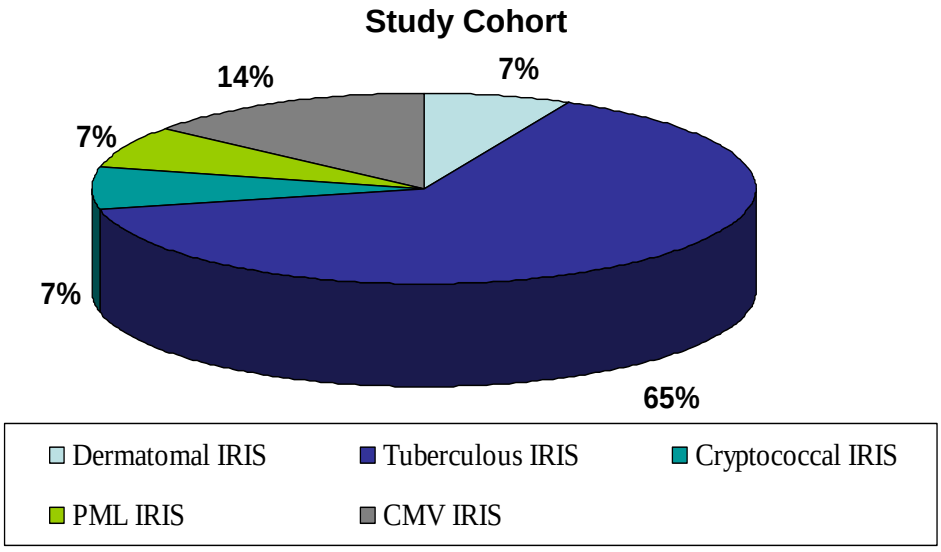
The majority of patient with IRIS in this study had not been previously diagnosed to have the same OI that caused the IRIS. In this study 5 patients with IRIS had previously been diagnosed to have the same opportunistic infection that caused the IRIS, in 4 cases the OI was different from the one diagnosed previously and in 5 cases OI had not been diagnosed previously. In all the cases where IRIS was due to the previously diagnosed OI, the underlying opportunistic infection was TB. This observation is consistent with report by Ratnam et al. that only 10 patients out of 44 patients who developed IRIS had prior opportunistic infections (24). All four patients with TB IRIS in this study had been treated for tuberculosis prior to initiation of HAART. Most studies on IRIS have not reported on occurrence of previous OIs.

The spectrum of opportunistic infections in this study was different from other cohorts in the following respects: (a) the rank order of the OIs causing IRIS in this study was TB (65%), CMV (14%), Cryptococcus (7%), PMLE (7%) and Herpes zoster (7%) in contrast to the study by Jevtovic et al where the rank order was dermatomal IRIS (51%) , Hepatitis C (23%), TB (12%), Hepatitis B (5%), CMV (5%), toxoplasma (2%), PML (2%) (see Figure 3); (b) TB was the cause of two-thirds of IRIS; (c) there were fewer patients with dermatological IRIS; (d) there were no patients with atypical mycobacterial IRIS, Hepatitis B and C related IRIS, Kaposi's sarcoma, toxoplasmosis and *Pneumocystis jirovecii* infection in our cohort. The lack of atypical mycobacteriosis IRIS may reflect the low background incidence of this infection in our cohort. Low rates of PCP and toxoplasmosis may be due to low background rates due to widespread use of cotrimoxazole prophylaxis. Low rates of Hepatitis B and C IRIS may reflect low background rates of HIV- Hepatitis B and C co-infection (the cohort had only one patient

with hepatitis B and no patients with HCV infection). The infrequent occurrence of Hepatitis B and C co-infection may reflect virtual absence of history of IV drug use among HIV patients presenting to our clinic. Other IRIS syndromes reported in the literature but not documented in our study were molluscum contagiosum, genital herpes simplex, tinea corporis, genital warts, cerebral toxoplasmosis and, Kaposi's sarcoma (22). This study suggests that the spectrum of IRIS is dependent on the background prevalence of opportunistic infections in the specific setting. In India in contrast to western settings IRIS is chiefly due to tuberculosis.

Figure 3. Spectrum of IRIS in our study in comparison with Jevtovic et al.





The frequency of TB IRIS in our study probably reflects the high burden of TB infection and disease in patients with HIV infection in our population. The overall incidence of TB IRIS in our cohort was 8%. The rates of TB IRIS have been variable between different studies. In retrospective cohort studies of patients initiated on HAART(22-24), the overall incidence of TB IRIS was low ranging between 0.8% and 2%. This may reflect the low background prevalence of tuberculosis in the population studied. There are other prospective studies on patients with HIV and TB co-infection which showed higher incidences of TB IRIS ranging between 15% and 37%(7, 27, 29). However, baseline CD4 counts were lower in these studies suggesting that these may have been groups with more advanced disease. In this study, 12% of patients with HIV-TB co-infection developed IRIS. This is almost twice the incidence reported by Kumaraswamy in Chennai of 7.6% (11/144) in patients with TB-HIV co-infection (28).

The following clinical observations can be made with regards to TB IRIS from this study:

a. Clinical presentations of TB IRIS were similar to descriptions from previous studies. The clinical presentations included tuberculous lymphadenitis, CNS TB, pulmonary tuberculosis, disseminated TB and skin TB.
b. Most patients presenting with TB-IRIS did not have previously diagnosed tuberculosis.
c. Clinical severity of TB-IRIS varied from transient lymphadenitis to severe CNS TB.
d. A high index of suspicion is necessary for the diagnosis of TB prior to initiation of HAART. In two patients who developed TB-IRIS, TB had been suspected prior to initiation of HAART but could not be confirmed.
e. Multi-organ involvement is common reflecting disseminated involvement of organs in HIV-TB co-infection: Three of 9 patients with TB IRIS had hepatic involvement (in the form of rising alkaline phosphatase or hepatomegaly) in addition to other organ involvement as part of IRIS. Liver biopsy from one patient demonstrated granulomatous inflammation confirming reinstated antigen specific T cell immunity.
f. Timing of HAART in relation to TB treatment does not appear to influence the incidence of IRIS. In this study, 17% and 27% of patients initiated on HAART within two months, and more than six months after initiation of ATT respectively developed IRIS. This data supports the decision analysis study advocating the early initiation of HAART in relation to TB treatment(52).

g. Outcome of treatment appears to be uniformly good. Most patients improved with treatment for tuberculosis. Both patients with CNS TB were also treated with steroids.

The clinical profile of CMV, cryptococcal, herpes zoster and PML IRIS in this study was similar to previous reports. CMV retinitis occurred in patients with CD4 counts below 50 cells/ml, consistent with findings in other studies. Dermatomal zoster occurred in patients with CD4 counts greater than 100cells/ml, which is also consistent with data reported in other studies(22-24).

Mean time to development of IRIS after intitiation of HAART was 33 days with the majority of cases occurring within two months. This was consistent with previously reported data. Kumarasamy et al. reported median time to IRIS as 42 days. In the retrospective cohort by French et al(23), 65% of IRIS cases occurred within 2 months of initiation of HAART while median time to IRIS was 7 weeks. In the study by Jevtovic et al.(22), the median time to IRIS was 4.6 months. Ratnam et al.(24) also described a median time to IRIS of 12 weeks. The later onset of IRIS in these studies may be due to the large proportion of patients with dermatomal IRIS in these cohorts, almost all of which occurred after two months. This may indicate that reconstitution of antigen specific immunity may occur at different points of time to different antigens. The shorter time to development of IRIS in our study may have been a result the prospective design, high index of suspicion and low rates of dermatological IRIS.

The mortality attributable to IRIS was low in our study. Only one patient with IRIS expired and this was probably due to drug toxicity. There was no mortality directly

attributable to IRIS. All patients improved on treatment for the underlying opportunistic infection and only two patients with CNS tuberculosis required treatment with steroids. Seven of 14 patients required hospital admission and the rest were treated as outpatients. This is consistent with data from other studies(22, 23). French et al reported death in only one out of 33 patients with IRIS(23). Manabe et al. reported a mortality of 10% in their case control study. However, this was a group of patients with higher disease morbidity as 92% of patients were inpatients, as hospital admission was one of the selection criteria in this study(38). Our results indicate that most patients with IRIS improve with treatment of the associated OI and the syndrome is not associated with high morbidity and mortality.

In this study, age, gender, baseline CD4 counts, absolute lymphocyte counts or mean body mass index (BMI) were not found to predict development of IRIS. This finding is different from other studies which have shown low baseline CD4 counts to predict development of IRIS(22, 23). These studies were retrospective, had larger sample size and greater proportion of patients with advanced immunodeficiency. The lack of association of low CD4 count with IRIS in this study may have been due to low IRIS event rates, smaller sample size and a smaller proportion of patients with very low CD4 counts. Timing of initiation of HAART was also not found to be predictive of IRIS in the entire cohort and as well as in patients with tuberculosis. This contrasts with the findings of Shelburne et al. who showed that in patients with mycobacterial opportunistic infections and cryptococcosis, early initiation of HAART was associated with greater risk of IRIS (26). The lack of association of timing of ART in this study may have been due to the smaller proportion who had a prior OI. Patients who had prior OIs had greater rates

of IRIS in our study although this was not statistically significant (p=0.09). Previous TB and disseminated TB were also not found to be significant risk factors. The lack of identifiable risk factors in this study may due to the heterogenous nature of the syndrome and the complex interplay between antigen burden, host immunity and genetic factors that has been referred to earlier. However, it is possible that larger studies may demonstrate significant predictive risk factors for IRIS.

In this study nearly all patients were treated with nevirapine and efavirenz based regimens as recommended by the National AIDS Control Organisation (NACO) guidelines and no patients were treated with PI based regimens. Among these regimens, the combination of drugs did not seem to influence the occurrence of IRIS. However four of five patients who were initiated on emtricitabine, tenofovir and efavirenz developed IRIS. The significance of this observation is unclear in view of small numbers. Observations from literature suggest that patients on boosted protease inhibitors(BPIs) are at greater risk for IRIS(38). The mechanisms by which BPIs are associated with IRIS may be related to a greater magnitude of rise in CD4 count as compared to other regimens (84) and immunomodulatory effects of PIs (85, 86), (87), (88). It is possible that the magnitude and rate of immune reconstitution may vary with different types of treatment and this may influence the development of IRIS.

The utility of the diagnostic criteria for IRIS in the Indian setting is evident in that all 14 cases fulfilled the diagnostic criteria. Only three cases of suspected IRIS did not fulfill diagnostic criteria.

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In summary, the incidence of IRIS in the cohort studied was 12.8%. The spectrum of IRIS in our study cohort was different from western studies, which indicates that the spectrum of IRIS in a region may be determined by the background rates of OIs specific to that population. TB IRIS was the most common type of IRIS. Presentation of TB IRIS was varied in clinical profile, timing and severity. Multi-organ involvement in TB IRIS was common. A high suspicion for tuberculosis may be required in patients being initiated on HAART as subclinical infection is common and may present as an IRIS if left untreated. Most patients presented within the first two months of treatment with HAART. IRIS in this study was associated with fairly good outcome with treatment of underlying OI. Baseline CD4 counts, age, BMI and WHO stage and timing of HAART in relationship to OIs did not predict development of IRIS. The majority of patients receiving emtricitabine, tenofovir and efavirenz developed IRIS but this needs to be interpreted with caution in view of small number of cases. The small sample size and loss to follow up are important limitations of this study. Further prospective studies are required to study the complexity of factors that determine the occurrence of IRIS in India

Conclusions

The important conclusions of this study are as follows:

1. 14 cases of IRIS were diagnosed in a cohort of 109 patients initiated on HAART with an incidence of 12.8% (CI- 7.2-20.6%).

2. TB was the most commonly identified IRIS in this study contributing to two thirds of all the IRIS (9/14 patients). This reflects the high burden of TB disease in our patients. 81.6% of all prior opportunistic infections in this cohort (40/49) were due to TB. There were no cases of MAC IRIS, Hepatitis B and C IRIS, reflecting the absence of these infections in this cohort of patients. The absence of Pneumocystis IRIS may reflect the low frequency of prior PCP infection (2 cases) in this cohort probably due to widespread use of TMP/SMX prophylaxis. Dermatological IRIS was also uncommon.

3. The majority of patients who developed IRIS had not previously been diagnosed to have the same opportunistic infection causing the IRIS (9/14 patients). It appears that sub-clinical opportunistic infections, particularly due to TB are common and difficult to clinically detect prior to initiation of HAART.

4. The clinical profile of TB, Cryptococcal, CMV, Herpes zoster and PMLE IRIS in this study was similar to previous reports. Of the nine patients with TB IRIS five presented with localised forms of TB, pulmonary, lymph node, meningitis and skin involvement and four presented with multi-organ system involvement.

5. Time to development of IRIS following initiation of HAART varied from 4-120 days with a mean of 33 days. 85% of patients developed IRIS within two months of initiation of HAART.

6. Twelve of 14 patients were managed with anti-infective treatment alone and 2 cases of TB meningitis were treated with steroids. The clinical outcomes of patients were uniformly good except for one patient with cryptococcal meningitis who died due to drug toxicity. There was no IRIS related mortality.

7. Clinical stage, BMI, baseline CD4 count, prior opportunistic infection, type of ART, timing of HAART treatment were not found to be significant risk factors in the development of IRIS.

8. The majority of patients on Efavirenz, emtricitabine and tenofovir developed IRIS (4/5 cases). This observation should be interpreted cautiously in view of the small numbers and requires further study.

In summary, IRIS is a clinically important syndrome in HIV patients initiated on HAART in the Indian setting. When compared to other studies, IRIS appears to be a

heterogeneous syndrome that varies with respect to event rates, opportunistic spectrum and clinical severity depending on the setting. This variability probably reflects the complex interaction between antigen burden, host immune response and genetic predisposing factors that underlie the pathophysiology of IRIS. In India, it is almost exclusively a result of exuberant immune response to widespread TB infection in patients with HIV infection. The lack of identifiable risk factors in this study may be due to heterogeneous nature of the syndrome and the complex interplay of factors that play a role in the underlying pathophysiology. Further studies are required to better delineate the pathophysiology of this syndrome and its predictors in the Indian setting.

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Abstract

Title of the abstract: Immune reconstitution inflammatory syndrome (IRIS): Incidence, characteristics and predictive factors among patients with HIV initiated on highly active anti-retroviral therapy (HAART)

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Objectives of the study:

To study the incidence and predictive factors of immune reconstitution inflammatory syndrome (IRIS) among a cohort of patients initiated on HAART and describe this syndrome among them.

Methods:

A cohort of patients with HIV infection initiated on HAART at Christian Medical College and Hospital and government ART centres was prospectively followed up for a minimum of six months to observe for the development of IRIS. Baseline CD4 cell counts, WHO staging of patients, BMI and presence of previous opportunistic infections were recorded in all patients. Overall incidence and opportunistic infection specific incidences of IRIS were calculated. Clinical presentations, investigations and outcome of patients with IRIS were recorded. Baseline characteristics were compared between patients who developed IRIS and those who did not, and predictors for IRIS were identified.

Results:

14 cases of IRIS were diagnosed in a cohort of 109 patients initiated on HAART with an incidence of 12.8% (CI- 7.2-20.6%). The incidence of individual IRIS syndromes were:

TB IRIS 8% (CI 3.8%, 15.1%), CMV IRIS 1.8% (CI 0.2%, 6.5%), Cryptococcal IRIS 1% (CI 0.02%,6.4%), PMLE IRIS 1% (CI 0.02%,6.4%) and Herpes zoster IRIS 1% (CI 0.02%,6.4%). The time to development of IRIS following initiation of HAART varied from 4-120 days with a mean of 33 days. 85% of patients developed IRIS within two months of initiation of HAART. In this study IRIS was associated with good outcomes. Clinical stage, BMI, baseline CD4 count, prior opportunistic infection, type of ART, timing of HAART treatment were not found to be significant risk factors in the development of IRIS.

Conclusions:

IRIS is an important clinical problem in this region which occurred at an incidence of 12.8% in this study. TB was the most common opportunistic infection presenting as IRIS which may be a reflection of the high prevalence of manifest or subclinical tuberculosis co-infection in patients with HIV being initiated on HAART in our setting. No significant predictors for IRIS were identified in this study. Outcomes in patients with IRIS appear to be fair with treatment of underlying opportunistic infections.

Appendix

IRIS patients: presentations

A detailed discussion of manifestations of various cases of IRIS along with diagnostic criteria, treatment and follow up is outlined below:

TB IRIS(Cases A - I)

Case A:

History and examination:

A 33 year old man with stage IV disease (wasting and AIDS dementia) with a baseline CD4 count of 8 cells/ml was initiated on a combination of Stavudine, lamivudine and Nevirapine. Two months later, he developed high grade fever and dry cough. On examination, he was icteric and had posterior cervical lymphadenopathy and hepatosplenomegaly. He had no history of tuberculosis in the past.

Investigations:

Ultrasound abdomen: Liver size increased to 17.6 cm from 14.9 cm on previous ultrasound. Splenomegaly of 13cm. New 6mm mesenteric lymph nodes not seen on previous ultrasound abdomen.

Liver function tests:

Liver function tests	Baseline	At time of worsening
Total bilirubin	0.5mg%	3.7mg%
Direct bilirubin	0.2mg%	3.1%
Total protein	8.4g%	5.9g%
Serum albumin	3.2g%	2.3g%
SGOT	60IU/ml	150IU/ml
SGPT	31IU/ml	90IU/ml
Alkaline phosphatise	139 IU/ml	634IU/ml

Chest X ray showed diffuse alveolar infiltrates.

Induced sputum was positive for acid fast bacilli.

His repeat CD4 count was 25 cells/ml.

Diagnosis:

Disseminated tuberculosis, IRIS.

Discussion:

This patient presented with paradoxical worsening following initiation of HAART. He had high grade fever, worsening hepatosplenomegaly, lymphadenopathy, new infiltrates on chest radiograph and rising alkaline phosphatase consistent with an inflammatory response involving multiple organs. Induced sputum showed acid fast bacilli, confirming the diagnosis. CD4 counts showed a rise from baseline. This patient had been noted to

have hepatomegaly at baseline screening prior to initiation of HAART. Hepatomegaly worsened and splenomegaly and intra-abdominal lymph nodes appeared after initiation of HAART. He had high grade fever with marked rise in alkaline phosphatase. This indicates that he had underlying tuberculosis which manifested following initiation of HAART. His course was atypical in acute onset with high grade fever, pulmonary, hepatic and lymph node involvement. This patient satisfied criteria for IRIS.

Treatment and follow up:

This patient was discharged on anti-tuberculous therapy and HAART. He improved on treatment and was well on follow up.

Case B:

History and examination:

A 32 year old man with clinical stage I HIV infection and CD4 count of 254 cells/ml was initiated on Zidovudine 300mg twice daily, Nevirapine 200mg once daily and Lamivudine 150mg twice daily. Four months later, he presented with a swelling in the left submandibular region. He had no associated fever or decreased appetite. He had never had tuberculosis in the past.

On examination, he had a 4.5 X 4.5cm swelling in the left submandibular region. The swelling was tender. There was no associated warmth or redness.

Investigations:

Fine needle aspiration from the submandibular lymph node showed epitheloid granulomas

CD4 count was 648 cells/ml.

Diagnosis:

Tuberculous lymphadenitis, Immune reconstitution inflammatory syndrome.

Discussion

This patients presented with all features of IRIS. He developed enlarged submandibular lymph nodes following initiation of HAART. He had features of an inflammatory response on histology. The clinical presentation was atypical in the localised presentation of lymphadenitis as well as the unusual site of involvement. Immune reconstitution was evident by the rise in CD4 count as well as presence of granulomas on fine needle aspiration of the lymph node suggesting a specific T cell response.

Treatment and follow up:

He was initiated on treatment for tuberculosis. The swelling gradually subsided on treatment. He was well on follow up.

Case C:

History and examination:

A 76 year old man with WHO stage IV HIV infection with a baseline CD4 on 168 cells/ml was initiated on lamivudine, nevirapine and stavudine combination therapy. One month later, he developed a 1 X 1 cm left supraclavicular lymph node swelling. He had no other systemic symptoms.

Investigations:

Lymph node biopsy: Caseating granulomatous inflammation consistent with tuberculosis. No acid fast bacilli were seen.

Diagnosis:

Tuberculous lymphadenitis; Immune reconstitution inflammatory syndrome.

Discussion:

This patient developed paradoxical worsening in the form of new onset lymphadenopathy following initiation of HAART. Immune reconstitution and inflammatory response was evidenced by granulomatous inflammation on lymph node biopsy. Localised presentation of lymphadenitis is an atypical presentation in an immunocompromised patient. He fits criteria for typical immune reconstitution inflammatory syndrome.

Follow up and treatment outcome:

He was initiated on Category I ATT and changed to an efavirenz based HAART regimen. The lymph node swelling subsided and he was well on subsequent follow up.

Case D:

History and examination:

A 49 year old lady with stage IV HIV infection and CD4 counts of 64 cells/ml was diagnosed to have sputum positive pulmonary tuberculosis with tuberculous lymphadenitis. A fine needle aspiration from an enlarged cervical lymph nodes showed one lymphohistiocytic aggregate. Six months later, she was initiated on stavudine, lamivudine and Nevirapine. Two months following initiation of HAART, she developed worsening lymphadenopathy and fever. She had a 2 X 2 cm palpable lymph node in the left middle deep cervical group of lymph nodes.

Investigations:

CD4 count at time of worsening:188 cells/ml.

Diagnosis:

Tuberculous lymphadenitis; Immune reconstitution inflammatory syndrome.

Discussion:

This patient had paradoxical worsening of a previous opportunistic infection while on HAART. Enlargement of cervical lymph nodes with high grade fever was consistent with

an inflammatory response. Localised presentation was atypical in an immunocompromised patient. Immune reconstitution was demonstrated by a rising CD4 count. She satisfied criteria for immune reconstitution inflammatory syndrome.

Follow up and outcome:

She was referred for a repeat fine needle aspiration of the lymph node. She has not followed up subsequently.

Case E:

History and examination:

A 28 year old lady was diagnosed to have TB meningitis with stage IV HIV infection when she was admitted to the hospital with fever, headache, vomiting and altered sensorium. Her CSF showed 110 cells with 65% lymphocytes, sugar of 29mg% with concomitant plasma glucose of 140 mg% and protein of 129 mg%. She was also noted to have cervical lymphadenopathy. Lymph node biopsy showed caseous necrosis bordered by confluent granulomas, epitheloid histiocytes and langhan's giant cells. Acid fast bacilli were present. She was initiated on category I ATT along with tapering steroids on which her symptoms improved. She was initiated on Stavudine, lamivudine and Nevirapine one month later. Her baseline CD4 count was 240 cells/ml. One month later, she presented to the emergency department with headache and vomiting. On

examination, she had neck stiffness. She was not in altered sensorium and had no history of fever or seizures.

Investigations:

CSF analysis: Cells: WBC 490/ul with 70% lymphcytes, protein 240 mg%, glucose 37 mg%. Cryptococcal smears and cultures were negative. Mycobacterial smears and cultures were negative.

Repeat CD4 counts: 617/ul.

Diagnosis:

Tuberculous meningitis; Immune reconstitution inflammatory syndrome.

Discussion:

This patient had paradoxical worsening of symptoms following initiation of HAART. She had been on treatment for tuberculous meningitis with documented improvement in symptoms prior to initiation of HAART. She had an atypical course of TB meningitis with paradoxical worsening following initial improvement in symptoms on treatment. Her CSF analysis showed an markedly cellular response. Immune reconstitution was evidenced by rising CD4 counts. This patient satisfied all criteria for IRIS.

Follow up and outcome:

She was continued on ATT and HAART and her symptoms improved without any further treatment.

Case F:

History and examination:

A 39 year old male with Stage IV HIV infection was diagnosed to have tuberculous meningitis when he presented to his local hospital with prolonged fever, headache and weight loss. His CSF showed elevated protein of 102mg% with low glucose of 48mg% and 7 cells all of which were lymphocytes. MRI showed multiple ring enhancing lesions suggestive of tuberculomas. He was initiated on ATT and tapering doses of steroids. His fever had subsided and other symptoms markedly improved. He was diagnosed to have HIV infection at this point of time and was referred to our centre for further treatment. His CD4 count at presentation was 40 cells/ml. Clinical examination was normal. Fundus was normal. He had no focal neurological deficits. There were no meningeal signs. He was initiated on HAART (Efavirenz 600mg once daily, Tenofovir 300mg once daily, Emtricitabline 200mg once daily) 24 days after initiating treatment for TB meningitis. Nine days later he developed fever associated with headache and vomiting. He developed altered sensorium and had one episode of generalised tonic clonic seizures.

On examination, his sensorium was altered. Fundus showed blurred margins. Neck stiffness was present. There were no focal deficits. He had hepatosplenomegaly.

Investigations:

CSF counts: 50 WBC/ul, 96% lymphocytes and 4% polymorphs

CSF protein: 89 mg%

Glucose: 47 mg%

CSF cultures: smears negative for acid fast bacilli. India ink examination negative.

Mycobacterial and fungal cultures did not show any growth.

Alkaline phosphatase: 592 IU/ml (baseline Alkaline phosphatase:160IU/ml)

Liver biopsy: Non-caseating granulomatous inflammation

Repeat CD4 count was 1020 cells/ml.

Diagnosis:

Tuberculous meningitis, Immune reconstitution inflammatory syndrome

Treatment:

He was continued on TB treatment, steroids as well as HAART. He developed efavirenz induced visual hallucinations. Therefore, his ART regimen was changed from an efavirenz to boosted protease inhibitor based regimen. On this he stopped having hallucinations. His fever and altered sensorium improved on treatment. He was well on follow up.

Discussion:

This patient had a typical IRIS. He developed paradoxical worsening soon after initiation of HAART. CSF showed an inflammatory response. Alkaline phosphatase levels increased. Liver biopsy confirmed granulomatous inflammation, indicative of a good cellular immune response. He had an atypical clinical presentation of TB meningitis with

paradoxical worsening following initial improvement with ATT and steroids. Hepatic involvement with marked elevation in alkaline phosphatase was also atypical. CD4 counts showed a marked rise, indicating immune reconstitution. This patient also developed drug toxicity further confusing his clinical picture. Drug toxicity may be difficult to distinguish from paradoxical worsening.

Case G:

History and examination:

A 38 year old lady with WHO stage III HIV infection diagnosed as sputum negative pulmonary tuberculosis on anti-TB treatment was initiated on HAART (Stavudine, lamivudine and efavirenz combination therapy) one month later. Two weeks following initiation of anti-retroviral therapy, she presented to the outpatient with fever, pruritis, jaundice and hepatosplenomegaly with a diffuse erythematous rash over the body. She was thought to have a drug rash. TB treatment was discontinued at the government hospital. Since the indication for initiation had been empirical, it was not continued. Her baseline CD4 had been 154 cells/ml. One month later, she presented with a tender subcutaneous swelling in the right thigh which subsequently ulcerated forming an ulcer 4 cm in diameter with undermined edges.

Investigations:

Ulcer edge biopsy: granulomatous inflammation consistent with tuberculosis. Repeat CD4 count: 418/ul.

Diagnosis:

Tuberculous ulcer, right thigh; Immune reconstitution inflammatory syndrome.

Discussion:

This patient had been diagnosed to have sputum negative pulmonary tuberculosis on the basis of a chest X ray showing bilateral miliary shadows. Following initiation of HAART, she developed skin rash, hepatitis and hepatosplenomegaly. Drug rash was considered and TB treatment was discontinued. After two months of initiation of HAART, she developed an ulcer on her right thigh, the biopsy from which showed granulomatous inflammation consistent with tuberculosis. This patient probably had inadequately treated disseminated tuberculosis and developed an immune reconstitution inflammatory syndrome following return of immunity towards persisting antigens. She satisfied all criteria for IRIS. Inflammation is clearly evidenced by granulomatous inflammation on biopsy and immune reconstitution by the marked rise in CD4 count from baseline. This is an atypical presentation with pulmonary involvement followed by localised skin involvement in the form of ulceration.

Follow up and outcome:

She was initiated on Category I ATT by RNTCP and Efavirenz based HAART regimen. Her ulcer healed over a period of three months. She was well on follow up.

Case H:

History and examination:

A 55 year old diabetic and hypertensive with HIV infection– WHO stage I disease and CD4 count of 161 cells/ml at initiation of HAART (emtricitabine, tenofovir and efavirenz) presented with history of fever five days after initiation of ART. The fever was high grade associated with cough with purulent expectoration. He had associated left-sided chest pain. There was no associated breathing difficulty. On examination, he was febrile. He was not in respiratory distress. Examination of the respiratory system was normal.

Investigations:

Total WBC count:	10,900/cu mm
Differential count:	85% neutrophils, 1% eosinophils, 8% lymphocytes and 6% monocytes.
Alkaline phosphatase:	151 IU/ml (baseline alkaline phosphatase: 92 IU/ml)

Chest X ray showed new infiltrates in the left lower zone.

Sputum for AFB:	Two smears showed a few acid fast bacilli
Repeat CD4 count:	162 cells/ml

Diagnosis:

Sputum positive pulmonary tuberculosis, Immune reconstitution inflammatory syndrome.

Treatment:

He was initiated on anti-TB treatment, which he took regularly. His symptoms improved and infiltrates completely resolved. He was well at follow up six months later.

Discussion:

This patient fits the criteria for IRIS. He had paradoxical worsening following initiation of HAART. He presented with acute onset cough, pleuritic chest pain, high grade fever, worsening chest infiltrates and sputum positivity for acid fast bacilli within one week following initiation of HAART. This is an atypical presentation of pulmonary tuberculosis. High grade fever with acute onset of symptoms were suggestive of an inflammatory response. Although, CD4 count did not show a significant rise, it is well known that viral load suppression occurs several weeks prior to rise in CD4 counts.

Case I:

A 38 year old man with stage IV HIV infection was initiated on Tab. Zidovudine 300mg twice daily, Tab. Lamivudine 150mg twice daily and Tab. Nevirapine 200mg twice daily. He had been diagnosed to have disseminated TB (US guided FNAC from peripancreatic lymph nodes showing granulomatous inflammation consistent with TB) eight months prior to initiation of HAART. He had been treated with regular ATT for six months. Baseline CD4 counts were 154 cells/ml. Fifteen days after initiating HAART, he

developed high grade fever with cough. Respiratory system examination was normal. Abdominal examination revealed that he had hepatosplenomegaly.

Investigations:

Sputum smears showed a few acid fast bacilli. Subsequent cultures grew Mycobacterium tuberculosis.

Chest X ray showed a left lower zone consolidation.

Repeat CD4 counts were 175 cells/ml.

Diagnosis and criteria:

Sputum positive pulmonary tuberculosis, immune reconstitution inflammatory syndrome.

Discussion:

This patient presented with a typical IRIS. He had paradoxical worsening after initiation of HAART. He had completed TB treatment and had been cured. Two weeks after starting HAART, he developed high grade fever and breathlessness associated with chest infiltrates and sputum acid fast bacilli positivity. High grade fever with breathlessness was consistent with an inflammatory response. He had an atypical course with an acute onset, lower zone consolidation and enlargement of liver and spleen. CD4 counts showed a modest increase consistent with immune reconstitution.

Treatment and follow up:

He was initiated on Category II ATT by RNTCP on which his symptoms improved. However, he was found to be persistently sputum positive after three months of regular Category II ATT. He was then treated for multi-drug resistant tuberculosis.

CMV IRIS (Cases J and K)

Case J:

History and examination:

A 29 year old man with stage IV disease was initiated on Tab. Stavudine 30mg twice daily, Lamivudine 150mg twice daily and Nevirapine 200mg once daily. His baseline CD4 was 7 cells/ml. He also had hepatitis B coinfection. He had been admitted with salmonella typhimurium septicaemia and Pneumocystis jirovecii pneumonia two weeks prior to initiation of HAART. He had also been diagnosed to have latent syphilis. Eleven days after initiation of HAART, he developed fever, cough and decreased vision in his right eye. Fundoscopy showed an appearance suggestive of CMV retinitis.

Investigations:

Repeat CD4 count 161 cells/ml

Diagnosis:

CMV retinitis, Immune reconstitution inflammatory syndrome

Discussion:

This patient had clinical deterioration following initiation of HAART. His presentation was not atypical. CMV uveitis and vitritis are atypical manifestations of CMV that often occur during immune reconstitution. However, CMV retinitis is also known to occur as an IRIS. He had an inflammatory response in the form of high grade fever associated with acute onset decrease in vision. CD4 counts showed a rise confirming immune reconstitution.

Follow up:

He was initiated on IV gancyclovir. His vision improved only marginally.

Case K:

History and examination:

A 43 year old female was diagnosed to have carcinoma breast for which she underwent simple mastectomy with axillary node sampling in January 2007. She had been on chemotherapy and had received four cycles of chemotherapy and external radiotherapy. She was diagnosed to have HIV infection (stage 4) at time of diagnosis of carcinoma breast. Her baseline CD4 counts were 42 cells/ml. She was diagnosed to have disseminated TB on 16/6/2007 when she presented with fever and hepatomegaly. Her CT thorax showed mediastinal lymphadenopathy with central hypodensities and she was empirically initiated on TB treatment. She became afebrile. She presented with dysphagia to the outpatient three weeks later. She was initiated on treatment with fluconazole for

probable oesophageal candidiasis. However, even after completion of two weeks of treatment, her symptoms continued to persist. An upper GI scopy at this point revealed circumferentially ulcerated mucosa with extensive sloughing. Biopsy taken showed an inflammatory exudate with necrotic material and candidal infestation. She was treated with amphotericin considering resistant oesophageal candidiasis. She was initiated on a combination of tenofovir, emtricitabine and efavirenz one month after onset of dysphagia (17/8/07). Two weeks following this she developed choking sensation and regurgitation while taking food. Fundus examination revealed peripheral CMV retinitis.

Investigations:

Endoscopy showed oesophageal ulceration with a tracheo-oesophageal fistula.

Biopsy was negative for inclusion bodies.

Serum CMV PCR positive

Serum CMV IgM antibody positive

Repeat CD4 counts: 131 cells/ml

Diagnosis:

CMV retinitis and probable CMV oesophagitis with tracheo-esophageal fistula; immune reconstitution inflammatory syndrome.

Discussion:

This patient presented with a typical IRIS. She had paradoxical worsening after initiation of HAART. Serial endoscopies demonstrated worsening ulceration of oesophagus with

development of a tracheo-oesophageal fistula which had not been present prior to initiation of HAART. Fundus examination revealed CMV retinitis, indicating a possible common etiology. This is an atypical presentation of CMV oesophagitis as a tracheo-oesophageal fistula. Oesophageal ulceration and development of a tracheo-oesophageal fistula is suggestive of marked inflammation. Immune reconstitution was evidenced by a rising CD4 count.

Treatment and outcome:

She was placed on an NG tube following which a feeding jejunostomy was done. As she had leucopenia, gancyclovir was not initiated. However, after 6 weeks of ART, her counts improved and CMV retinitis resolved spontaneously. She was discharged to continue jejunostomy feeds. She was discharged on anti-tuberculous therapy and HAART.

Herpes Zoster IRIS

Case L:

History and examination:

A 38yr old man with stage I HIV infection and CD4 count of 177 cells/ml was initiated on Tab. Efavirenz 600mg once daily Tenofovir 300mg once daily and Emtricitabline 200mg once daily. Twenty seven days later he developed vesicular lesions associated with pain over his chest in the T7 and T8 dermatomes.

Investigations:

CD4 at time of deterioration: 626 cells/ml

Diagnosis:

Dermatomal herpes zoster, Immune reconstitution inflammatory syndrome.

Discussion:

This patient had a typical IRIS. He developed localised dermatomal herpes zoster following initiation of HAART associated with severe pain. He had features of an inflammatory response in the form of severe associated pain. Localised herpes zoster is an atypical presentation of zoster in an immunocompromised patient. Repeat CD4 counts demonstrated marked immune reconstitution.

Follow up and treatment:

He was initiated on Acyclovir. Lesions healed within 15 days. He was well on follow up.

Cryptococcal IRIS

Case M

History and examination:

A 38 year old man with a baseline CD4 count of 119 cells/ml and stage I HIV infection was initiated on ART (Zidovudine 300mg twice daily, Lamivudine 150mg twice daily and Nevirapine 200mg twice daily). He presented to the emergency department three

months later with severe headache, vomiting, high grade fever and altered sensorium. He had meningeal signs. He had bilateral papilloedema on fundoscopy.

Investigations:

CSF counts: Total WBC count 170/ul, 90% lymphocytes, 10% polymorphs; glucose 34 mg%; protein 84 mg%.

CSF smear: yeast like organisms.

CSF culture: Cryptococcus neoformans.

CT brain: Mild hydrocephalus.

LFT:

Total bilirubin: 1.6mg%

Direct bilirubin: 0.7mg%

Total protein: 6.5g%

Serum albumin: 2.8g%

SGOT: 197 IU/ml

SGPT: 234 IU/ml

Alkaline phospatase: 201 IU/ml

Diagnosis:

Cryptococcal meningitis; Immune reconstitution inflammatory syndrome.

Discussion:

This patient presented with paradoxical worsening three months following initiation of anti retroviral therapy. He was diagnosed to have cryptococcocal meningitis. Elevated CSF counts were suggestive of an inflammatory response. Repeat CD4 counts were not available to confirm immune reconstitution. Acute deterioration in symptoms and presence of meningeal signs with a cellular response was an atypical presentation of cryptococcal meningitis. This clinical picture is consistent with an immune reconstitution inflammatory syndrome.

Follow up and outcome:

He was initiated on amphotericin B which was discontinued due to renal failure and persistent hypokalemia. He had a sudden cardiac arrest which was probably secondary to amphotericin induced hypokalemia.

PMLE IRIS:

Case N:

History and examination:

A 45 year old man with clinical stage IV HIV infection had presented to the outpatient with imbalance on walking for 2 months. This was insidious in onset. He had history of falling towards the left. This was associated with slurring of speech. He had history of chronic alcohol consumption for ten years which he had stopped at onset of symptoms. He also had history of TB lymphadenitis in 2005 for which he had received TB treatment

for eight months regularly. A diagnosis of probable alcohol related cerebellar dysfunction was made. His CD4 count was 116 cells/ml. He was initiated on Nevirapine 200mg bd, Zidovudine 300mg bd and Lamivudine 150mg bd. He presented to the emergency department with worsening symptoms 3 days later. He had significant worsening of his ataxia. He was unable to stand or walk. He had increased slurring of speech. He was admitted and evaluated. On examination, he had bilateral nystagmus, past pointing (more on the left side) and dysdiachokinesia. He also had decreased sensation over the left side of the face.

Investigations:

CD4 levels: 151 cells/ml

Serum B12 levels 224 pg/ml

Folate levels >24ng/ml

Cerebrospinal fluid: total WBC 2/cu mm, all lymphocytes, RBC 90(30% crenation), protein 47mg% and glucose level 58mg%

Cerebrospinal fluid cultures negative for bacterial, mycobacterial and fungal growth.

Cerebrospinal VDRL negative

MRI brain: Long TR hyperintensity in left cerebellar matter extending into ipsilateral middle and superior cerebellar peduncles and dorsal part of left side of pons. A smaller hyperintensity visualised in the right superior cerebellar white matter and cerebellar peduncles. Multiple patchy long TR hyperintensities in left centrum semi-ovale and posterior periventricular region. No appreciable enhancement seen on the post contrast study. Features in favour of cerebellar demyelination.

Ultrasound abdomen: Normal. No evidence of chronic liver disease

Diagnosis:

Progressive multifocal leukoencephalopathy, Immune reconstitution inflammatory syndrome.

Discussion:

This patient had paradoxical worsening following initiation of HAART in the form of acute worsening of cerebellar symptoms and signs with dysarthria. MRI showed cerebellar demyelination extending into the left pons consistent with a diagnosis of PML. This presentation was atypical as he developed sudden worsening of symptoms that had been progressing insidiously over a period of two months. Immune reconstitution was evidenced by a rising CD4 count. Therefore,this patient satisfied all criteria for IRIS.

Follow up:

HAART was continued. His condition gradually improved. He was well at six months follow up with significant improvement in deficits.

Patients with paradoxical worsening but did not fulfill the criteria for IRIS

Case O:

History and examination:

A 41 year old lady with stage IV disease and CD4 count of 88 cells/ml was initiated on Zidovudine 300mg twice daily, Lamivudine 150mg twice daily and Efavirenz 600mg once daily. This was changed to a stavudine based regimen two months later when she developed anemia. She had history of chronic large bowel diarrhoea since 2005 with weight loss. Stool examination for parasites had been negative. She had been diagnosed to have pulmonary TB three months ago (perihilar lymphadenopathy on CT thorax) and had been initiated on ATT which she was taking regularly. Three months after initiating HAART, she presented with severe headache, vomiting, fever for three days with altered sensorium for one day. She had one episode of generalised tonic clonic seizures in the emergency department. On examination, she had neck stiffness. She was unresponsive. Her pupils were dilated and fixed. Dolls eye was absent. Fundoscopy showed papilloedema.

Investigations:

CT brain: marked cerebral edema with basal meningeal enhancement and focal hypodensities in both occipital regions suggestive of cerebritis.

Chest X ray: Left sided ill defined infiltrates.

Total WBC count: 17500/ul with 1% myelocytes, 1% metamyelocytes, 4% band forms, 82% neutrophils, 9% lymphocytes and 3% monocytes.

Liver function tests:

Total bilirubin: 0.4mg%

Direct bilirubin: 0.2mg%

Total protein: 7.6g%

Serum albumin: 2.9g%

SGOT: 16 IU/ml

SGPT: 83 IU/ml

Alkaline phospatase: 180 IU/ml

Electrolytes:

Serum sodium: 123meq/dl

Potassium: 3.4meq/dl

Bicarbonate: 3meq/dl

Creatinine 4.1mg%

Haemoglobin: 8mg%

Prothrombin time: 16.9 seconds

Activated thromboplastin time: 43 seconds

Arterial blood gas:

pH: 6.77

Blood cultures: negative for growth

Repeat CD4 count: 116 cells/ml

Discussion:

This patient presented paradoxical worsening following initiation of HAART. She had features suggestive of meningo-encephalitis. Lumbar puncture was not done due to features of high intracranial pressure. She had a high peripheral blood count with a left shift. She had multiorgan dysfunction with severe metabolic acidosis. Chest X ray showed an ill-defined left sided infiltrate. Differential diagnosis included pneumococcal meningitis, tuberculous meningitis and fungal meningitis. However, the acute presentation, high counts and multi-organ dysfunction were more in favour of a pyogenic meningitis. She was initiated on crystalline penicillin, anti-tuberculous and anti-fungal therapy. However, her condition did not improve. Prognosis was discussed with relatives and supports were withdrawn. She expired within three days. Although this patient presented with paradoxical worsening following initiation of HAART, the diagnosis of IRIS could not be confirmed.

Case P

History and examination:

A 40 year old man was diagnosed to have tuberculous lymphadenitis and stage III HIV infection with CD4 counts of 124/ul. He was initiated on a combination of lamivudine, Stavudine and Efavirenz two weeks later. Ten days following initiation of HAART he presented with history of high grade fever for one week associated with chills and rigors. On examination, his liver was palpable 2cm below the right costal margin. There was no splenomegaly or lymphadenopathy.

Investigations:

Total WBC count: 5400/ul, 79% neutrophils, 1% eosinophils, 9% monocytes and 11% lymphocytes.

Liver function tests:

Total bilirubin: 0.5mg%

Direct bilirubin: 0.2mg%

Total protein: 8.5g%

Serum albumin: 3.2g%

SGOT: 45 IU/ml

SGPT: 45 IU/ml

Alkaline phospatase: 88 IU/ml

Blood cultures: No growth

Malarial smears: negative

Scrub typhus IgM ELISA: negative

Leptospira IgM ELISA: negative

Typhidot: negative

Dengue IgM: negative

Repeat CD4:169 cells/ml

Discussion:

This patient had paradoxical worsening following initiation of HAART. He had been diagnosed to have tuberculous lymphadenitis for which he was on treatment. He presented with fever and hepatomegaly. Evaluation for the fever was negative. His fever subsided without any specific treatment. This patient does not satisfy criteria for IRIS. Although he had an episode of paradoxical worsening following initiation of HAART, this was not clearly attributable to his underlying opportunistic infection. High grade fever was suggestive of an inflammatory response. Immune reconstitution was demonstrated by a rise in CD4 count. However, all criteria for IRIS were not satisfied.

Follow up and outcome:

This patient was well on six months follow up.

Case Q:

History and examination:

A 40 year old man with WHO stage III HIV infection with baseline CD4 counts of 61 cells/ml was diagnosed to have sputum positive pulmonary tuberculosis for which he was treated with category I anti-tuberculous therapy (DOTS). Following completion of six

months of treatment, he was initiated on Zidovudine, Lamivudine and Nevirapine. Following initiation of HAART, he developed itchy papular lesions over the back. A diagnosis of probable scabies was made. He was treated with ivermectin with which lesions resolved.

Discussion:

This patient had paradoxical worsening following initiation of HAART. However, immune reconstitution was not demonstrated. This patient does not satisfy criteria for IRIS. Scabies has not been documented as an IRIS in the literature.

Follow up and outcome:

The patient was well at follow up.

S..no	Name	sex	age	hosp no.	CD4	WHO stage	ALC	ht	wt	BMI	date of HAA	place of HA	Prev OI?
1	Appa Rao	M	51	875687C	100	3	2340	167	76	27.25089	11/4/2006	CMC	Y
2	MEEna	F	30	146379C	190	1	840	150	50	22.22222	11/4/2006	CMC	N
3	Gandhi	F	33	919802C	49	4	1036	143	40	19.56086	12/2/2006	CMC	Y
4	Bhasker	M	37	746868C	45	4	177	158	45	18.02596	11/1/2006	CMC	Y
5	Murugan	M	33	453561C	198	3	3102	161	61	23.53304	2/21/2007	ED	N
6	Sri Ram	M	52	915830C	113	3	1575	175	45	14.69388	11/15/2006	CMC	N
7	Sudhir Kun	M	40	888760C	162	4	2436	167	47	16.85252	11/15/2006	CMC	N
8	Uma Shanl	M	40	919689c	34	4	360	164	42	15.6157	11/9/2006	CMC	N
9	Ananthalak	F	40	909260C	77	4	264	156	35	14.38199	11/17/2006	CMC	Y
10	Kumar S	M	37	308781c	91	4	689	168	41	14.52664	12/3/2006	ED	Y
11	Ramesh	M	43	949854c	185	1	1650	172	64	21.63332	1/3/2007	ED	N
12	Pitchandi	M	37	953095c	48	3	600	175	75	24.4898	1/24/2007	CMC	Y
13	Dr. Jued Ai	M	33	960639C	27	4	720	158	60	24.03461	1/23/2007	CMC	Y
14	Kamalam	F	33	898496c	111	1	693	156	39	16.02564	2/14/2007	CMC	N
15	Vijaykumar	F	39	401630C	240	1	1836	170	48	16.609	1/8/2007	CMC	N
16	Raju DRC	M	39	925526C	68	4	600	168	64	22.67574	12/21/2006	CMC	Y
17	Jamuna	F	41	609862C	88	4	1504	150	41	18.22222	6/12/2007	ED	Y
18	Velangini	F	40	648049C	215	1	1829	163	54	20.32444	2/5/2007	ED	N
19	Himagirish	M	34	953847C	179	3	2034	163	53	19.94806	3/7/2007	ED	N
20	Mahendrar	M	46	046235B	209	1	2214	165	71	26.07897	2/21/2007	CMC	N
21	Renuka	F	36	975795C	10	1	767	146	46	21.58003	3/10/2007	ED	N
22	Manogarar	M	53	897763C	236	3	2085	175	65	21.22449	3/7/2007	CMC	N
23	Parimala	F	25	163989c	279	2	861	155	61	25.39022	3/14/2007	CMC	Y
24	Kalaiselvar	M	42	843529C	61	3	1880	160	52	20.3125	12/20/2006	CMC	N
25	Kumar Raj	M	40	934658C	155	1	2852	180	80	24.69136	2/14/2007	CMC	N
26	Selladurai	M	42	903114C	105	1	780	169	63	22.05805	1/10/2007	CMC	N
27	Kamala V	F	57	951153C	36	4	144	150	56	24.88889	1/4/2007	CMC	Y
28	Hema Bind	F	28	962977C	187	1	1504	155	40	16.64932	2/20/2007	CMC	N
29	Tamil Selvi	F	44	989092C	125	2	2254	146	51	23.92569	3/13/2007	CMC	N
30	Chandraka	F	32	668652C	179	1	1400	157	48	19.47341	3/27/2007	CMC	N
31	Karuna M	F	37	464999C	122	1	1760	172	52	17.57707	4/7/2007	ED	N
32	Sivaya	M	47	977099C	36	4	752	160	53	20.70313	2/27/2007	CMC	Y
33	Jayachand	M	30	419035C	254	1	2340	167	76	27.25089	2/6/2007	CMC	N
34	Damodarar	M	47	521373C	255	1	1512	173	83	27.7323	3/13/2007	CMC	N
35	Anita Pal	F	27	101530C	268	1	1652	150	62	27.55556	11/29/2006	CMC	N

36	Chandrase	M	38	720082C	119	1	468	165	75	27.54821	4/18/2007	CH	N
37	Thenmozhi	F	26	92888C	119	1	900	153	45	19.22338	3/28/2007	CMC	N
38	Mahesh K	M	33	994350C	119	1	1920	175	58	18.93878	2/28/2007	TIR	N
39	Parasuram	M	40	984239C	118	4	540				4/10/2007	ED	Y
40	Indira	F	36	652471B	94	4	1404	165	44	16.16162	5/16/2007	ED	N
41	Ranganath	M	38	802697C	212	1	2310	165	56	20.56933	5/22/2007	CMC	N
42	Rani G	F	36	998352C	44	4	44	156	36	14.7929	4/13/2007	Athoor	Y
43	Samudrala	M	29	988933C	7	4	560	170	35	12.11073	3/19/2007	CMC	Y
44	Shivamani	M	34	968987C	135	1	2024	171	62	21.20311	4/26/2007	ED	N
45	Nand Kisho	M	55	000838D	161	1	872	170	59	20.41522	4/5/2007	CMC	N
46	Jayaraman	M	46	777345C	252	2	2340	168	59	20.9042	5/2/2007	CMC	N
47	Dil Shad	F	35	016300D	40	2	968	159	50	19.7777	5/4/2007	CMC	N
48	Prakash	M	30	017296D	75	2	154	166	57	20.68515	5/12/2007	TIR	N
49	Kumar G	M	35	499155B	52	1	3420	162	63	24.00549	6/6/2007	CMC	N
50	Sellamal	F	67	042207D	148	1	828	146	50	23.45656	6/13/2007	CMC	N
51	Garudacha	M	40	047080D	61	3	931	158	46	18.42653	6/22/2007	CMC	Y
52	Kumari	F	29	050437D	75	1	1716	153	58	24.7768	6/27/2007	CMC	N
53	Gopal	M	40	051627B	249	3	1088	159	55	21.75547	8/6/2007	ED	N
54	Ravi Shank	M	45	062480D	116	4	960	165	40	14.69238	7/20/2007	CMC	Y
55	Bhumanan	F	38	058837D	154	3	1122	153	43	18.369	8/31/2007	TIR	Y
56	Sanjoy Mo	M	34	992022C	218	1	1140	171	63	21.54509	8/22/2007	CMC	N
57	Raju GS	M	31	908110C	346	3	2706	156	62	25.47666	6/14/2007	TIR	Y
58	Siva Prasa	M	55	105530C	309	1	2356	170	78	26.98962	1/5/2007	CMC	N
59	Ramesh S	M	38	893199C	190	3	1386	174	76	25.10239	11/1/2006	CMC	Y
60	Shanti	F	37	984485C	52	4	2448	151	34	14.91163	3/16/2007	CMC	N
61	Subramani	M	54	005743D	60	4	700	165	56	20.56933	5/9/2007	CMC	Y
62	Viswanath	M	38	030704D	177	1	4459	165	68	24.97704	6/7/2007	CMC	N
63	Kannan	M	55	079647D	151	1	1274	163	60	8/29/2007	8/29/2007	CMC	N
64	Suresh Bal	M	32	039249D	135	1	744	170	75	25.95156	8/1/2007	CH	N
65	Srinivasa R	M	40	036722D	71	4	1368	167	58	20.79673	7/18/2007	CMC	Y
66	Ponnaiyan	M	39	007185D	165	4	2106	167	57	20.43817	5/2/2007	CMC	N
67	Mohana Ku	M	35	072659d	182	4	1311	170	53	18.3391	9/5/2007	CMC	Y
68	Chandrase	M	36	059506D	24	4	450	170	52	17.99308	8/22/2007	Cud	Y
69	Nithur	M	33	027814D	69	4	1224	160	28	10.9375	10/3/2007	CMC	Y
70	Prassanna	F	43	949385C	42	4	180	155	55	22.89282	10/3/2007	CMC	Y
71	Anitha	F	29	054988D	36	4	1000	146	40	18.76525	9/26/2007	ED	N

72	Arjunan	M	38	957015C	157	4	1170	173	52	17.37445	9/1/2007	Coim	Y
73	Samadhan	F	38		99	1	1260	166	72	26.12861	10/3/2007	CMC	N
74	Fouzia	F	31	380058B	196	1	1120	150	63	28	9/5/2007	CMC	N
75	Kalpana V	F	29	016950D	72	4	1296	160	55	21.48438	5/23/2007	CMC	N
76	Chinmoy	M	30	986182C	109	4	1600		63	#DIV/0!	3/9/2007	CMC	Y
77	Krishna M	M	29	884539C	186	3	180	161	52	20.06095	2/14/2007	Tir	Y
78	Hiradaya	M	51	954331C	109	4	416	163	61	22.95909	4/1/2007	CMC	N
79	Tamil Selvi	F	45	989092C	125	1	2254	146	51	23.92569	3/13/2007	CMC	N
80	Anand Bab	M	37	370333C	51	3	1134		54	#DIV/0!	3/13/2007	CMC	N
81	Ashish Kur	M	39	023906D	40	3	336	170	66	22.83737	5/18/2007	CMC	Y
82	Venugopal	M	33	922626C	241	1	2769	173	56	18.71095	10/31/2007	CMC	N
83	Nagabhoos	M	40	239758c	183	1	1833		74	#DIV/0!	11/16/2006	TIR	Y
84	Ananthi	F	31	896338B	184	1	988	165	47	17.26354	10/12/2007	ED	Y
85	Jamuna	F	45	897228C		4	1260	143	33	16.13771	3/7/2007	ED	Y
86	Obul R	M	30	951030C	253	4	1736	169	49	17.15626	2/1/2007	Cud	Y
87	Hema N	F	32	091909D	8	4	882	154	43	18.13122	10/1/2007	Tir	Y
88	Elappan	M	38	521991C	280	2	2848	170	75	25.95156	10/18/2007	ED	N
89	Pandu Ran	M	30	984892C	200	3	1484	169	50	17.50639	11/12/2007	ED	Y
90	Saravanan	M	32	352062C	229	2	2944	170	80	27.68166	10/4/2007	ED	Y
91	Chitti Babu	M	37	536199C	96	4	672	163	52	19.57168	10/23/2007	ED	Y
92	Senthil Kur	M	34	851286C	229	3	3290	170	70	24.22145	11/2/2007	SAL	Y
93	SambaMoo	M	40	702981C	71	3	969		61	#DIV/0!	10/12/2007	CMC	Y
94	Basheer Al	M	33	288229C	161	2	2006	174	73	24.11151	11/1/2007	ED	N
95	Deenadaya	M	34	818077B	10	4	372	162	44	16.76574	11/3/2007	CMC	Y
96	Lalitha	F	46	105512D	67	4	918	153	45	19.22338	10/31/2007	CMC	N
97	Srinivasan	M	42	104880d	89	4	1584	156	54	22.18935	10/27/2007	Cud	N
98	Kannu P	M	76	818065C	168	4	1140	174	50	16.51473	8/7/2007	CMC	Y
99	Jothi S	M	58	971713C	227	1	781	168	70	24.80159	7/7/2007	CMC	Y
100	Munindra	M	40	101515D	124	3	594	173	56	18.71095	10/15/2007	CMC	Y
101	Sabita Dey	M	48	016754D	64	4	484	165	56	20.56933	5/1/2007	CMC	N
102	Vijaykumar	M	33	171596C	8	4	605	168	40	14.17234	10/11/2007	CMC	N
103	Annalakshi	F	23	348543C		4	999	142	33	16.3658	9/21/2007	ED	N
104	Isaac	M	64	975684C	98	4	960	168	50	17.71542	4/30/2007	TIR	Y
105	Srinivasan	M	36	756645C	106	4	2160	159	49	19.38214	7/1/2007	Cud	Y
106	Padmanab	M	29	998133C	73	1	798	165	59	21.67126	3/29/2007	Tir	N
107	Shanta Ma	F	45	017497d	118	4	1640	157	45	18.25632	10/26/2007	Coim	Y

108	Indra	F	28	118371D	240	4	1125	150	37	16.44444	11/14/2007	ED	Y
109	Rani C	F	49	994498C	64	4	1044	155	43	17.89802	11/12/2007	ED	Y

previous O	date of diagı	treatment	ongoing?	no. of days	type of HA	IRIS Y/N	last visit	days of follı	years of fol	follow up complete
1.1	8/21/2006	ATT	Y	75.00	3	N	7/31/2007	269.00	0.5	Y
					4	N	3/7/2007	123.00	0.5	Y
4	11/3/2006		N	29.00	1	N	6/5/2007	185.00	0.5	Y
1.4	1/17/2006	ATT	N	288.00	1	N	10/24/2007	357.00	0.5	Y
					2	N	10/10/2007	231.00	0.5	Y
					1	N	6/13/2007	210.00	0.5	Y
					4	N	11/19/2007	369.00	0.5	Y
					4	N	5/22/2007	194.00	0.5	Y
4	11/2/2006	Gan	Y	15.00	1	N	1/5/2007	49.00	0.134247	N
1.1	3/1/2006	ATT	N	277.00	?	N	1/3/2007	31.00	0.084932	N
					3	N	1/17/2007	14.00	0.038356	N
1.4	1/4/2007	ATT	Y	20.00	4	N	4/11/2007	77.00	0.210959	Exp
1.2	9/1/2006	ATT	Y	144.00	4	N	9/7/2007	227.00	0.5	Y
					1	N	9/5/2007	203.00	0.5	Y
					1	N	3/10/2008	427.00	0.5	Y
1.4	11/17/2006	ATT	Y	34.00	3	N	4/16/2008	482.00	0.5	Y
1.2	3/21/2007	ATT	Y	83.00	2	?	9/12/2007	92.00	0.252055	Exp
					2	N	4/21/2008	441.00	0.5	Y
					1	N	9/29/2007	206.00	0.5	Y
					1	N	1/23/2008	336.00	0.5	Y
					1	N	9/5/2007	179.00	0.5	Y
					1	N	8/1/2007	147.00	0.5	Y
1.1	1/1/2002	ATT	N	1898.00	4	N	4/16/2008	399.00	0.5	Y
					3	N	12/26/2007	371.00	0.5	Y
					1	N	7/19/2007	155.00	0.5	Y
					1	N	8/24/2007	226.00	0.5	Y
1.1	12/20/2006	ATT	Y	15.00	3	N	2/1/2007	28.00	0.076712	Y
					1	N	11/27/2007	280.00	0.5	Y
					1	N	9/19/2007	190.00	0.5	Y
					2	N	9/8/2007	165.00	0.5	Y
					2	N	10/17/2007	193.00	0.5	Y
1.5	12/1/2006	ATT	Y	88.00	3	N	11/21/2007	267.00	0.5	Y
					1	Y	6/20/2007	134.00	0.5	Y
					1	N	2/8/2008	332.00	0.5	Y
					1	N	4/19/2008	507.00	0.5	Y

						2	Y	8/8/2007	112.00	0.306849	Exp
						1	N	12/5/2007	252.00	0.5	Y
						2	N	9/12/2007	196.00	0.5	Y
	1.2	3/13/2007	ATT	Y	28.00	?	N	3/19/2008	344.00	0.5	Y
						2	N	10/31/2007	168.00	0.5	Y
						2	N	11/28/2007	190.00	0.5	Y
	1.4	4/4/2007	ATT	Y	9.00	?	N	5/20/2007	37.00	0.1	Exp
	3	3/5/2007	Bac	N	14.00		1	Y	12/12/2007	268.00	0.5	Y
							2	N	4/15/2008	355.00	0.5	Y
							5	Y	4/28/2007	23.00	0.5	Y
							1	N	1/27/2008	270.00	0.5	Y
							1	N	4/16/2008	348.00	0.5	Y
							2	N	6/15/2007	34.00	0.093151	N
							2	N	2/20/2008	259.00	0.5	Y
							2	N	2/13/2008	245.00	0.5	Y
	1.2	12/15/2006	ATT	N	189.00		1	?	1/20/2008	212.00	0.5	Y
							1	N	7/31/2007	34.00	0.093151	N
							2	N	3/21/2008	228.00	0.5	Y
	1.1	1/1/2005	ATT	N	930.00		2	Y	4/21/2008	276.00	0.5	Y
	1.4	7/25/2007	ATT	Y	37.00		3	Y	4/16/2008	229.00	0.5	Y
							2	N	9/7/2007	16.00	0.043836	N
	1.4	3/1/2007	ATT	Y	105.00		3	N	4/16/2008	307.00	0.5	Y
							3	N	10/24/2007	292.00	0.5	Y
	1.3	9/20/2006	ATT	Y	42.00		4	N	4/8/2008	524.00	0.5	Y
							1	N	9-Apr	390.00	0.5	Y
	3	4/11/2007	Bac	Y	28.00		1	N	4/8/2008	335.00	0.5	Y
							5	Y	7/4/2007	27.00	0.073973	Y
							2	N	3/19/2008	203.00	0.5	Y
							2	N	4/16/2008	259.00	0.5	Y
	1.4	6/9/2007	ATT	Y	39.00		5	N	2/6/2008	203.00	0.5	Y
							1	N	4/16/2008	350.00	0.5	Y
	1.4	7/26/2007	ATT	Y	41.00		3	N	5/1/2008	0.00	0.5	Y
	1.1	7/18/2007	ATT	Y	35.00		3	N	12/26/2007	126.00	0.345205	N
	1.4	5/23/2007	ATT	Y	133.00		3	N	10/26/2007	13.00	0.03	N
5/1.4		7/1/2007	ATT/flu	Y	94.00		5	Y			0.5	Y
							1	N	3/26/2008		0.5	Y

1.4	1/11/2007	ATT	N	233.00	2	Y	2/6/2008	158.00	0.5	Y
					1	N	4/23/2008	203.00	0.5	Y
					2	N	9/26/2007	21.00	0.057534	N
					2	N	10/17/2007	147.00	0.5	Y
7	3/2/2007	acyc	N	7.00	3	N	6/5/2007	88.00	0.241096	N
8	9/15/2006	Bac	N	152.00	2	N	5/11/2007	86.00	0.235616	N
					1	N	4/18/2007	17.00	0.046575	N
					1	N	12/4/2007	266.00	0.5	Y
					1	N	27-Nov	259.00	0.5	Y
1.6	4/25/2007	ATT	Y	23.00	5	Y	3/9/2008	296.00	0.5	Y
					2	N	1/30/2008	91.00	0.249315	N
1.1	1/1/2002	ATT	N	1780.00	2	N	10/3/2007	321.00	0.5	Y
1.1	3/22/2007	ATT	N	204.00	1	N	4/2/2008	173.00	0.5	Y
1.4	10/11/2006	ATT	Y	147.00	3	N	3/14/2007	7.00	0.019178	N
8	12/27/2006	Bac	N	36.00 ?		N	4/3/2008	427.00	0.5	Y
1.4	9/28/2007	ATT		3.00 ?		N	4/15/2008	197.00	0.5	Y
					1	N	1/9/2008	83.00	0.227397	N
1.1	3/7/2007	ATT	N	250.00	2	N	4/16/2008	156.00	0.5	Y
1.1	9/3/2007	ATT	Y	31.00	2	N	4/23/2008	202.00	0.5	Y
1.4	3/22/2007	ATT	Y	215.00	4	N	3/3/2008	132.00	0.361644	N
1.3	9/17/2007	ATT	Y	46.00 ?		N	4/29/2008	179.00	0.5	Y
1.7	9/11/2007	ATT	Y	31.00	3	N	2/20/2008	131.00	0.358904	N
					1	N	4/29/2008	180.00	0.5	Y
1.8	3/8/2007	ATT	Y	240.00	3	N	1/30/2008	88.00	0.241096	N
					2	N	4/8/2008	160.00	0.5	Y
					2	N	4/30/2008	186.00	0.5	Y
5	5/6/2006	flu	N	458.00	2	Y	4/23/2008	260.00	0.5	Y
7	6/3/2006	acyc	N	399.00	2	N	4/2/2008	270.00	0.5	Y
1.1	9/29/2007	ATT	Y	16.00	2	?	5/1/2008	199.00	0.5	Y
					3	N	9/19/2007	141.00	0.5	Y
					1	Y	12/26/2007	76.00	0.208219	Y
					2	N	4/23/2008	215.00	0.5	Y
1.7	3/21/2007	ATT	Y	40.00 ?		N	4/30/2008	366.00	0.5	Y
1.4	3/14/2007	ATT	Y	109.00 ?		N	4/30/2008	304.00	0.5	Y
					2	N	4/30/2008	398.00	0.5	Y
1.1	7/25/2007	ATT	Y	93.00	2	N	1/9/2008	75.00	0.205479	N

1.6	10/22/2007	ATT	N	23.00	1	Y	12/18/2007	34.00	0.093151	Y
1.2	4/11/2007	ATT	N	215.00	1	Y	4/8/2008	148.00	0.5	Y

Name	Hosp no.	age	sex	Stage	CD41	CD42	VL1	VL2
Arjunan	957015C	38	M	4	154	175		
Gaudachal	047080C	40	M	3	61	?		
Jamuna	609862C	41	F	4	88	116		
Jayachand	419035c	32	M	1	254	648		
Samudrala	988933C	29	M	4	7	161		
Viswanath	030704D	38	M	1	177	626		
Ravi Shanl	062480D	45	M	4	116	151		
Ashish K	023906D	39	M	3	40	1020		
Nandkisho	000838D	55	M	1	161	162		
Munindra	101515D	40	M	3	124	169		
Indra	118371D	28	F	4	240	617		
Kannu P	818065C	76	M	4	168	?		
Prasanna	949385C	43	F	4	42	131		
Bhuminani	058837D	38	F	3	154	418		
Vijaykuma	171596C	33	M	4	8	25		
Chandrase	720082C	38	M	1	119	?		
Rani C	994498C	49	F	4	64	188		

ALC base	wt	ht	BMI	prev OI Y/N	type of OI 1	type of OI2	date of OI	Date of ART
1170	52	173	17.37445	Y	1.40		1/11/2007	9/1/2007
931	46	158	18.42653	Y	1.2		12/15/2006	6/22/2007
1504	41	150	18.22222	Y	1.1	8	3/21/2007	6/12/2007
2340	76	167	27.25089	N				2/20/2007
560	39	157	15.82214	Y	3		3/5/2007	3/19/2007
4459	68	165	24.97704	N				6/7/2007
960	40	164	14.8721	Y	1.1		1/1/2005	7/20/2007
336	66	170	22.83737	Y	1.6		4/25/2007	5/18/2007
872	59	170	20.41522	N				4/5/2007
594	56	173	18.71095	Y	1.1		9/29/2007	10/15/2007
1125	37	150	16.44444	Y	1.6		10/22/2007	11/14/2007
1140	50	174	16.51473	Y	5	7	5/6/2006	8/7/2007
180	55	160	21.48438	Y	5	1.4	7/6/2007	8/17/2007
1122	43	153	18.369	Y	1.8		7/25/2007	8/31/2007
	40	168	14.17234	N				10/31/2007
468	75	165	27.54821	N				4/18/2007
1044	43	155	17.89802	Y	1.2		4/11/2007	11/12/2007
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Date of IRIS	ART-OI	IRIS-ART	type of IRIS	Imp/died	IRIS/IRSLS	type of ART
9/16/2007	233	15	1.40	Imp	Y	2
6/29/2007		7	6.00	Imp	?	2
8/28/2007	83	77	?TBM	died	?	2
6/20/2007		120	1.1	Imp	Y	2
4/27/2007	14	39	4	imp	Y	1
7/4/2007		27	7	Imp	Y	5
7/24/2007	930	4	9	Imp	Y	2
5/24/2007	23	6	1.4/1.6	Imp	Y	5
4/10/2007		5	1.2	Imp	Y	5
10/20/2007	16	5	1.1	Imp	?	4
12/18/2007	23	34	1.6	Imp	Y	1
9/5/2007	458	29	1.1	Imp	Y	2
9/1/2007	42	15	4.1	Imp	Y	5
31/9/2007	37	30	1.9	Imp	Y	3
12/26/2007		56	1.4	Imp	Y	1
4/25/2007		7	10.0	died	Y	2
2/8/2008	215	88	1.1	?	Y	1
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